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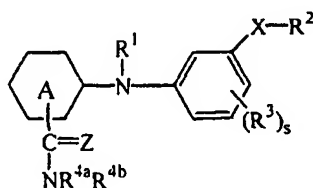
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(54) Title: AMIDE DERIVATIVES AS GLYCOGEN SYNTHASE KINASE 3-BETA INHIBITORS

WO 03/037869 A1



(I')

(57) Abstract: This invention concerns a compound of formula (I')
, a N-oxide, a pharmaceutically acceptable addition salt, a quaternary
amine and a stereochemically isomeric form thereof, wherein ring A
represents a 6-membered heterocycle; R¹ is hydrogen; aryl; formyl;
C₁₋₆alkylcarbonyl; optionally substituted C₁₋₆alkyl; C₁₋₆alkyloxy; optionally substituted C₁₋₆alkyloxyC₁₋₆alkylcarbonyl; X is a direct bond or
a linker atom or group; Z is O or S; R² is hydrogen, C₁₋₁₀alkyl, C₂₋₁₀alkenyl,
C₂₋₁₀alkynyl, a carbocycle or a heterocycle, each of said groups may
optionally be substituted; R³ is hydrogen; hydroxy; halo; optionally
substituted C₁₋₆alkyl or C₂₋₆alkenyl or C₂₋₆alkynyl; C₁₋₆alkyloxy; C₁₋₆alkylthio; C₁₋₆alkyloxyalkyl; C₁₋₆alkylcarbonyloxy;
carboxyl; cyano; nitro; amino; mono- or di(C₁₋₆alkyl)amino; polyhaloC₁₋₆alkyl; polyhaloC₁₋₆alkyloxy; polyhaloC₁₋₆alkylthio;
R²¹; R²¹-C₁₋₆alkyl; R²¹-O-; R²¹-S-; R²¹-C(=O)-; R²¹-S(=O)_p-; R²¹-S(=O)_p-NH-; R²¹-S(=O)_p-NH-; R²¹-C(=O)-;
-NHC(=O)H; -C(=O)NHNH₂; R²¹-C(=O)-NH-; R²¹-C(=O)-NH-; -C(=NH)R²¹; -C(=NH)R²¹; R^{4a} or R^{4b} each independently represent
hydrogen, R⁸, -Y₁-NR⁹-Y₂-NR¹⁰, -Y₁-NR⁹-Y₁-R⁸, -Y₁-NR⁹-Y₁-R⁸; provided that -X-R² and/or R³ is other than hydrogen; their use,
pharmaceutical compositions comprising them and processes for their preparation.

**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB,

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

AMIDE DERIVATIVES AS GLYCOGEN SYNTHASE KINASE 3-BETA INHIBITORS

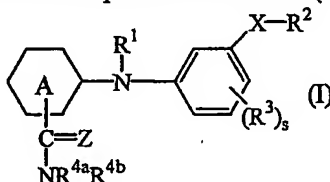
The present invention concerns a novel group of compounds, their use as a medicine,
 5 their use for the manufacture of a medicament for the treatment of diseases mediated
 through glycogen synthase kinase 3, in particular glycogen synthase kinase 3 β ;
 processes for their preparation and pharmaceutical compositions comprising them.

WO 97/19065 discloses substituted 2-anilinopyrimidines useful as p56^{lck}, p59^{lyn},
 10 ZAP-70 and protein kinase C inhibitors.
 WO 00/62778 describes cyclic protein tyrosine kinase inhibitors.

The present invention relates to compounds which are distinguishable from the prior art
 in structure, pharmacological activity, potency or selectivity.

15

The present invention concerns a compound of formula (I)



a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a
 stereochemically isomeric form thereof, wherein

20 Z represents O or S;

ring A is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl;

R¹ is hydrogen; aryl; formyl; C₁₋₆alkylcarbonyl; C₁₋₆alkyl; C₁₋₆alkyloxycarbonyl;

C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl,

C₁₋₆alkylcarbonyloxy; C₁₋₆alkyloxyC₁₋₆alkylcarbonyl optionally substituted with

25 C₁₋₆alkyloxycarbonyl;

X is -NR¹-; -NH-NH-; -N=N-; -O-; -C(=O)-; -C(=S)-; -O-C(=O)-; -C(=O)-O-;

-O-C(=O)-C₁₋₆alkyl-; -C(=O)-O-C₁₋₆alkyl-; -O-C₁₋₆alkyl-C(=O)-;

-C(=O)-C₁₋₆alkyl-O-; -O-C(=O)-NR¹-; -NR¹-C(=O)-O-; -O-C(=O)-C(=O)-;

-C(=O)-NR¹-; -NR¹-C(=O)-; -C(=S)-NR¹-; -NR¹-C(=S)-; -NR¹-C(=O)-NR¹-;

30 -NR¹-C(=S)-NR¹-; -NR¹-S(=O)-NR¹-; -NR¹-S(=O)₂-NR¹-; -C₁₋₆alkyl-C(=O)-NR¹-;

-O-C₁₋₆alkyl-C(=O)-NR¹-; -C₁₋₆alkyl-O-C(=O)-NR¹-; -C₁₋₆alkyl-; -O-C₁₋₆alkyl-;

-C₁₋₆alkyl-O-; -NR¹-C₁₋₆alkyl-; -C₁₋₆alkyl-NR¹-; -NR¹-C₁₋₆alkyl-NR¹-;

-NR¹-C₁₋₆alkyl-C₃₋₇cycloalkyl-; -C₂₋₆alkenyl-; -C₂₋₆alkynyl-; -O-C₂₋₆alkenyl-;

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-C₂₋₆alkenyl-O-; -NR¹-C₂₋₆alkenyl-; -C₂₋₆alkenyl-NR¹-; -NR¹-C₂₋₆alkenyl-NR¹-;
 -NR¹-C₂₋₆alkenyl-C₃₋₇cycloalkyl-; -O-C₂₋₆alkynyl-; -C₂₋₆alkynyl-O-;
 -NR¹-C₂₋₆alkynyl-; -C₂₋₆alkynyl-NR¹-; -NR¹-C₂₋₆alkynyl-NR¹-;
 -NR¹-C₂₋₆alkynyl-C₃₋₇cycloalkyl-; -O-C₁₋₆alkyl-O-; -O-C₂₋₆alkenyl-O-;
 5 -O-C₂₋₆alkynyl-O-; -CHOH-; -S-; -S(=O)-; -S(=O)₂-; -S(=O)-NR¹-; -S(=O)₂-NR¹-;
 -NR¹-S(=O)-; -NR¹-S(=O)₂-; -S-C₁₋₆alkyl-; -C₁₋₆alkyl-S-; -S-C₂₋₆alkenyl-;
 -C₂₋₆alkenyl-S-; -S-C₂₋₆alkynyl-; -C₂₋₆alkynyl-S-; -O-C₁₋₆alkyl-S(=O)₂- or a direct
 bond;

R² is hydrogen, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, R²⁰, each of said groups
 10 representing R² may optionally be substituted where possible with one or more
 substituents each independently being selected from =S; =O; R¹⁵; hydroxy; halo;
 nitro; cyano; R¹⁵-O-; SH; R¹⁵-S-; formyl; carboxyl; R¹⁵-C(=O)-; R¹⁵-O-C(=O)-;
 R¹⁵-C(=O)-O-; R¹⁵-O-C(=O)-O-; -SO₃H; R¹⁵-S(=O)-; R¹⁵-S(=O)₂-; R⁵R⁶N;
 R⁵R⁶N-C₁₋₆alkyl; R⁵R⁶N-C₃₋₇cycloalkyl; R⁵R⁶N-C₁₋₆alkyloxy; R⁵R⁶N-C(=O)-;
 15 R⁵R⁶N-C(=S)-; R⁵R⁶N-C(=O)-NH-; R⁵R⁶N-C(=S)-NH-; R⁵R⁶N-S(=O)_n-;
 R⁵R⁶N-S(=O)_n-NH-; R¹⁵-C(=S)-; R¹⁵-C(=O)-NH-; R¹⁵-O-C(=O)-NH-;
 R¹⁵-S(=O)_n-NH-; R¹⁵-O-S(=O)_n-NH-; R¹⁵-C(=S)-NH-; R¹⁵-O-C(=S)-NH-;
 R¹⁷R¹⁸N-Y_{1a}-; R¹⁷R¹⁸N-Y₂-NR¹⁶-Y₁-; R¹⁵-Y₂-NR¹⁹-Y₁-; H-Y₂-NR¹⁹-Y₁-;
 R³ is hydrogen; hydroxy; halo; C₁₋₆alkyl; C₁₋₆alkyl substituted with cyano, hydroxy or
 20 -C(=O)R⁷; C₂₋₆alkenyl; C₂₋₆alkenyl substituted with one or more halogen atoms or
 cyano; C₂₋₆alkynyl; C₂₋₆alkynyl substituted with one or more halogen atoms or
 cyano; C₁₋₆alkyloxy; C₁₋₆alkylthio; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxy;
 carboxyl; cyano; nitro; amino; mono- or di(C₁₋₆alkyl)amino; polyhaloC₁₋₆alkyl;
 polyhaloC₁₋₆alkyloxy; polyhaloC₁₋₆alkylthio; R²¹; R²¹-C₁₋₆alkyl; R²¹-O-; R²¹-S-;
 25 R²¹-C(=O)-; R²¹-S(=O)_p-; R⁷-S(=O)_p-; R⁷-S(=O)_p-NH-; R²¹-S(=O)_p-NH-;
 R⁷-C(=O)-; -NHC(=O)H; -C(=O)NHNH₂; R⁷-C(=O)-NH-; R²¹-C(=O)-NH-;
 -C(=NH)R⁷; -C(=NH)R²¹;

R^{4a} or R^{4b} each independently are hydrogen, R⁸, -Y₁-NR⁹-Y₂-NR¹⁰R¹¹, -Y₁-NR⁹-Y₁-R⁸,
 -Y₁-NR⁹R¹⁰;

30 R⁵ and R⁶ each independently are hydrogen, R⁸, -Y₁-NR⁹-Y₂-NR¹⁰R¹¹, -Y₁-NR⁹-Y₁-R⁸,
 -Y₁-NR⁹R¹⁰, or

R⁵ and R⁶ may together with the nitrogen to which they are attached form a saturated or
 partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8
 membered monocyclic heterocycle, each of said heterocycles may optionally be
 35 substituted with one or more substituents selected from R¹², R¹³ and R¹⁴, or each of
 said heterocycles may optionally be fused with a benzene ring, said benzene ring

being optionally substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;

R^7 is C_{1-6} alkyl, C_{1-6} alkyloxy, amino, mono- or di(C_{1-6} alkyl)amino or polyhalo C_{1-6} alkyl;

R^8 is C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; C_{1-6} alkyl substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic, bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic saturated heterocycle or with a monocyclic, bicyclic or tricyclic partially saturated heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of said groups representing R^8 may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;

R^9 , R^{10} and R^{11} each independently are hydrogen or R^8 , or

any two of R^9 , R^{10} and R^{11} may together be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby forming a saturated or partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8 membered monocyclic heterocycle together with the nitrogen atoms to which they are attached, each of said heterocycles may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;

R^{12} , R^{13} and R^{14} each independently are hydrogen; R^{15} ; hydroxy; halo; nitro; cyano; R^{15} -O-; SH; R^{15} -S-; formyl; carboxyl; R^{15} -C(=O)-; R^{15} -O-C(=O)-; R^{15} -C(=O)-O-; R^{15} -O-C(=O)-O-; $-SO_3H$; R^{15} -S(=O)-; R^{15} -S(=O)₂-; $R^{15}R^{16}N$ -S(=O)-; $R^{15}R^{16}N$ -S(=O)₂-; $R^{17}R^{18}N$ -Y₁-; $R^{17}R^{18}N$ -Y₂-NR¹⁶-Y₁-; R^{15} -Y₂-NR¹⁹-Y₁-; H-Y₂-NR¹⁹-Y₁-; oxo, or

any two of R^{12} , R^{13} and R^{14} may together be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby forming a saturated or partially saturated monocyclic 3 to 8 membered carbo - or heterocycle or an aromatic 4 to 8 membered monocyclic carbo - or heterocycle together with the atoms to which they are attached, or

any two of R^{12} , R^{13} and R^{14} may together be $-O-(CH_2)_r-O-$ thereby forming a saturated, partially saturated or aromatic monocyclic 4 to 8 membered carbo - or heterocycle together with the atoms to which they are attached;

R^{15} is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated

heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; C₁₋₆alkyl substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic, bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic saturated heterocycle or with a monocyclic, bicyclic or tricyclic partially saturated heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of said substituents representing R¹⁵ may optionally be substituted with one or more substituents selected from R¹², R¹³ and R¹⁴; or each of said carbocycles or heterocycles may optionally be fused with a benzene ring, said benzene ring being optionally substituted with one or more substituents selected from R¹², R¹³ and R¹⁴; R¹⁶, R¹⁷, R¹⁸ and R¹⁹ each independently are hydrogen or R¹⁵, or R¹⁷ and R¹⁸, or R¹⁵ and R¹⁹ may together be C₁₋₆alkanediyl or C₂₋₆alkenediyl thereby forming a saturated or partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8 membered monocyclic heterocycle, each of said heterocycles may optionally be substituted with one or more substituents selected from R¹², R¹³ and R¹⁴; or R¹⁷ and R¹⁸ together with R¹⁶ may be C₁₋₆alkanediyl or C₂₋₆alkenediyl thereby forming a saturated or partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8 membered monocyclic heterocycle together with the nitrogen atoms to which they are attached, each of said heterocycles may optionally be substituted with one or more substituents selected from R¹², R¹³ and R¹⁴; R²⁰ is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; R²¹ is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle, each of said carbocycles or heterocycles representing R²¹ may optionally be substituted with one or more substituents selected from R¹², R¹³ and R¹⁴; Y_{1a} is -Y₃-S(=O)-Y₄-; -Y₃-S(=O)₂-Y₄-; -Y₃-C(=O)-Y₄-; -Y₃-C(=S)-Y₄-; -Y₃-O-Y₄-; -Y₃-S-Y₄-; -Y₃-O-C(=O)-Y₄- or -Y₃-C(=O)-O-Y₄-;

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Y_1 or Y_2 each independently are a direct bond, $-Y_3-S(=O)-Y_4-$; $-Y_3-S(=O)_2-Y_4-$,
 $-Y_3-C(=O)-Y_4-$, $-Y_3-C(=S)-Y_4-$, $-Y_3-O-Y_4-$, $-Y_3-S-Y_4-$, $-Y_3-O-C(=O)-Y_4-$ or
 $-Y_3-C(=O)-O-Y_4-$;

Y_3 or Y_4 each independently are a direct bond, C_{1-6} alkanediyl, C_{2-6} alkenediyl or

5 C_{2-6} alkynediyl;

n is 1 or 2;

m is 1 or 2;

p is 1 or 2;

r is 1 to 5;

10 s is 1 to 3;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each
independently selected from halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, cyano,

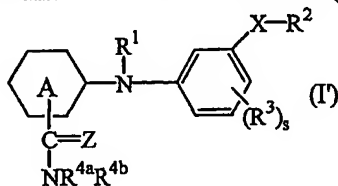
nitro, polyhalo C_{1-6} alkyl and polyhalo C_{1-6} alkyloxy;

provided that $-X-R^2$ and/or R^3 is other than hydrogen; and

15 provided that the following compounds

N-methoxy-*N*-methyl-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinecarboxamide
and *N*-phenyl-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinecarboxamide are not
included.

20 The present invention also relates to the use of a compound for the manufacture of a
medicament for the prevention or the treatment of diseases mediated through GSK3,
said compound being a compound of formula of formula (I')



25 a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a
stereochemically isomeric form thereof, wherein

Z represents O or S;

ring A is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl;

R^1 is hydrogen; aryl; formyl; C_{1-6} alkylcarbonyl; C_{1-6} alkyl; C_{1-6} alkyloxycarbonyl;

30 C_{1-6} alkyl substituted with formyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl,
 C_{1-6} alkylcarbonyloxy; C_{1-6} alkyloxy C_{1-6} alkylcarbonyl optionally substituted with
 C_{1-6} alkyloxycarbonyl;

X is $-NR^1-$; $-NH-NH-$; $-N=N-$; $-O-$; $-C(=O)-$; $-C(=S)-$; $-O-C(=O)-$; $-C(=O)-O-$;

$-O-C(=O)-C_{1-6}$ alkyl-; $-C(=O)-O-C_{1-6}$ alkyl-; $-O-C_{1-6}$ alkyl- $C(=O)-$;

- $-C(=O)-C_{1-6}alkyl-O-$; $-O-C(=O)-NR^1-$; $-NR^1-C(=O)-O-$; $-O-C(=O)-C(=O)-$;
 $-C(=O)-NR^1-$; $-NR^1-C(=O)-$; $-C(=S)-NR^1-$; $-NR^1-C(=S)-$; $-NR^1-C(=O)-NR^1-$;
 $-NR^1-C(=S)-NR^1-$; $-NR^1-S(=O)-NR^1-$; $-NR^1-S(=O)_2-NR^1-$; $-C_{1-6}alkyl-C(=O)-NR^1-$;
 $-O-C_{1-6}alkyl-C(=O)-NR^1-$; $-C_{1-6}alkyl-O-C(=O)-NR^1-$; $-C_{1-6}alkyl-$; $-O-C_{1-6}alkyl-$;
5 $-C_{1-6}alkyl-O-$; $-NR^1-C_{1-6}alkyl-$; $-C_{1-6}alkyl-NR^1-$; $-NR^1-C_{1-6}alkyl-NR^1-$;
 $-NR^1-C_{1-6}alkyl-C_{3-7}cycloalkyl-$; $-C_{2-6}alkenyl-$; $-C_{2-6}alkynyl-$; $-O-C_{2-6}alkenyl-$;
 $-C_{2-6}alkenyl-O-$; $-NR^1-C_{2-6}alkenyl-$; $-C_{2-6}alkenyl-NR^1-$; $-NR^1-C_{2-6}alkenyl-NR^1-$;
 $-NR^1-C_{2-6}alkenyl-C_{3-7}cycloalkyl-$; $-O-C_{2-6}alkynyl-$; $-C_{2-6}alkynyl-O-$;
 $-NR^1-C_{2-6}alkynyl-$; $-C_{2-6}alkynyl-NR^1-$; $-NR^1-C_{2-6}alkynyl-NR^1-$;
10 $-NR^1-C_{2-6}alkynyl-C_{3-7}cycloalkyl-$; $-O-C_{1-6}alkyl-O-$; $-O-C_{2-6}alkenyl-O-$;
 $-O-C_{2-6}alkynyl-O-$; $-CHOH-$; $-S-$; $-S(=O)-$; $-S(=O)_2-$; $-S(=O)-NR^1-$; $-S(=O)_2-NR^1-$;
 $-NR^1-S(=O)-$; $-NR^1-S(=O)_2-$; $-S-C_{1-6}alkyl-$; $-C_{1-6}alkyl-S-$; $-S-C_{2-6}alkenyl-$;
 $-C_{2-6}alkenyl-S-$; $-S-C_{2-6}alkynyl-$; $-C_{2-6}alkynyl-S-$; $-O-C_{1-6}alkyl-S(=O)_2-$ or a direct
bond;
- 15 R^2 is hydrogen, $C_{1-10}alkyl$, $C_{2-10}alkenyl$, $C_{2-10}alkynyl$, R^{20} , each of said groups
representing R^2 may optionally be substituted where possible with one or more
substituents each independently being selected from $=S$; $=O$; R^{15} ; hydroxy; halo;
nitro; cyano; $R^{15}-O-$; SH ; $R^{15}-S-$; formyl; carboxyl; $R^{15}-C(=O)-$; $R^{15}-O-C(=O)-$;
 $R^{15}-C(=O)-O-$; $R^{15}-O-C(=O)-O-$; $-SO_3H$; $R^{15}-S(=O)-$; $R^{15}-S(=O)_2-$; R^5R^6N ;
20 $R^5R^6N-C_{1-6}alkyl$; $R^5R^6N-C_{3-7}cycloalkyl$; $R^5R^6N-C_{1-6}alkyloxy$; $R^5R^6N-C(=O)-$;
 $R^5R^6N-C(=S)-$; $R^5R^6N-C(=O)-NH-$; $R^5R^6N-C(=S)-NH-$; $R^5R^6N-S(=O)_n-$;
 $R^5R^6N-S(=O)_n-NH-$; $R^{15}-C(=S)-$; $R^{15}-C(=O)-NH-$; $R^{15}-O-C(=O)-NH-$;
 $R^{15}-S(=O)_n-NH-$; $R^{15}-O-S(=O)_n-NH-$; $R^{15}-C(=S)-NH-$; $R^{15}-O-C(=S)-NH-$;
 $R^{17}R^{18}N-Y_{1a}-$; $R^{17}R^{18}N-Y_2-NR^{16}-Y_1-$; $R^{15}-Y_2-NR^{19}-Y_1-$; $H-Y_2-NR^{19}-Y_1-$;
25 R^3 is hydrogen; hydroxy; halo; $C_{1-6}alkyl$; $C_{1-6}alkyl$ substituted with cyano, hydroxy or
 $-C(=O)R^7$; $C_{2-6}alkenyl$; $C_{2-6}alkenyl$ substituted with one or more halogen atoms or
cyano; $C_{2-6}alkynyl$; $C_{2-6}alkynyl$ substituted with one or more halogen atoms or
cyano; $C_{1-6}alkyloxy$; $C_{1-6}alkylthio$; $C_{1-6}alkyloxycarbonyl$; $C_{1-6}alkylcarbonyloxy$;
carboxyl; cyano; nitro; amino; mono- or di($C_{1-6}alkyl$)amino; polyhalo $C_{1-6}alkyl$;
30 polyhalo $C_{1-6}alkyloxy$; polyhalo $C_{1-6}alkylthio$; R^{21} ; $R^{21}-C_{1-6}alkyl$; $R^{21}-O-$; $R^{21}-S-$;
 $R^{21}-C(=O)-$; $R^{21}-S(=O)_p-$; $R^7-S(=O)_p-$; $R^7-S(=O)_p-NH-$; $R^{21}-S(=O)_p-NH-$;
 $R^7-C(=O)-$; $-NHC(=O)H$; $-C(=O)NHNH_2$; $R^7-C(=O)-NH-$; $R^{21}-C(=O)-NH-$;
 $-C(=NH)R^7$; $-C(=NH)R^{21}$;
 R^{4a} or R^{4b} each independently are hydrogen, R^8 , $-Y_1-NR^9-Y_2-NR^{10}R^{11}$, $-Y_1-NR^9-Y_1-R^8$,
35 $-Y_1-NR^9R^{10}$;
 R^5 and R^6 each independently are hydrogen, R^8 , $-Y_1-NR^9-Y_2-NR^{10}R^{11}$, $-Y_1-NR^9-Y_1-R^8$,
 $-Y_1-NR^9R^{10}$, or

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- R^5 and R^6 may together with the nitrogen to which they are attached form a saturated or partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8 membered monocyclic heterocycle, each of said heterocycles may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} , or each of
 5 said heterocycles may optionally be fused with a benzene ring, said benzene ring being optionally substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;
- R^7 is C_{1-6} alkyl, C_{1-6} alkyloxy, amino, mono- or di(C_{1-6} alkyl)amino or polyhalo C_{1-6} alkyl; R^8 is C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; a monocyclic, bicyclic or tricyclic saturated
 10 carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; C_{1-6} alkyl substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a
 15 monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic, bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic saturated heterocycle or with a monocyclic, bicyclic or tricyclic partially saturated heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of
 20 said groups representing R^8 may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;
- R^9 , R^{10} and R^{11} each independently are hydrogen or R^8 , or any two of R^9 , R^{10} and R^{11} may together be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby forming a saturated or partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8 membered monocyclic heterocycle together with the nitrogen
 25 atoms to which they are attached, each of said heterocycles may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;
- R^{12} , R^{13} and R^{14} each independently are hydrogen; R^{15} ; hydroxy; halo; nitro; cyano; R^{15} -O-; SH; R^{15} -S-; formyl; carboxyl; R^{15} -C(=O)-; R^{15} -O-C(=O)-; R^{15} -C(=O)-O-; R^{15} -O-C(=O)-O-; -SO₃H; R^{15} -S(=O)-; R^{15} -S(=O)₂-; $R^{15}R^{16}N$ -S(=O)-; $R^{15}R^{16}N$ -S(=O)₂-; $R^{17}R^{18}N$ -Y₁-; $R^{17}R^{18}N$ -Y₂-NR¹⁶-Y₁-; R^{15} -Y₂-NR¹⁹-Y₁-; H-Y₂-NR¹⁹-Y₁-; oxo, or
 30 any two of R^{12} , R^{13} and R^{14} may together be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby forming a saturated or partially saturated monocyclic 3 to 8 membered carbo – or heterocycle or an aromatic 4 to 8 membered monocyclic carbo – or heterocycle
 35 together with the atoms to which they are attached, or

- any two of R^{12} , R^{13} and R^{14} may together be $-O-(CH_2)_r-O-$ thereby forming a saturated, partially saturated or aromatic monocyclic 4 to 8 membered carbo- or heterocycle together with the atoms to which they are attached;
- 5 R^{15} is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; C_{1-6} alkyl substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a
- 10 monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic, bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic saturated heterocycle or with a monocyclic, bicyclic or tricyclic partially saturated heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of said substituents representing R^{15} may optionally be substituted with one or more
- 15 substituents selected from R^{12} , R^{13} and R^{14} ; or each of said carbocycles or heterocycles may optionally be fused with a benzene ring, said benzene ring being optionally substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;
- R^{16} , R^{17} , R^{18} and R^{19} each independently are hydrogen or R^{15} , or R^{17} and R^{18} , or R^{15} and R^{19} may together be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby
- 20 forming a saturated or partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8 membered monocyclic heterocycle, each of said heterocycles may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ; or
- R^{17} and R^{18} together with R^{16} may be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby forming
- 25 a saturated or partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8 membered monocyclic heterocycle together with the nitrogen atoms to which they are attached, each of said heterocycles may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;
- R^{20} is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle;
- 30, R^{21} is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle;
- 35 R^{21} is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle;

bicyclic or tricyclic aromatic heterocycle, each of said carbocycles or heterocycles representing R^{21} may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;

Y_{1a} is $-Y_3-S(=O)-Y_4-$; $-Y_3-S(=O)_2-Y_4-$, $-Y_3-C(=O)-Y_4-$, $-Y_3-C(=S)-Y_4-$, $-Y_3-O-Y_4-$,

5 $-Y_3-S-Y_4-$, $-Y_3-O-C(=O)-Y_4-$ or $-Y_3-C(=O)-O-Y_4-$;

Y_1 or Y_2 each independently are a direct bond, $-Y_3-S(=O)-Y_4-$; $-Y_3-S(=O)_2-Y_4-$,

$-Y_3-C(=O)-Y_4-$, $-Y_3-C(=S)-Y_4-$, $-Y_3-O-Y_4-$, $-Y_3-S-Y_4-$, $-Y_3-O-C(=O)-Y_4-$ or

$-Y_3-C(=O)-O-Y_4-$;

Y_3 or Y_4 each independently are a direct bond, C_{1-6} alkanediyl, C_{2-6} alkenediyl or

10 C_{2-6} alkynediyl;

n is 1 or 2;

m is 1 or 2;

p is 1 or 2;

r is 1 to 5;

15 s is 1 to 3;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, cyano,

nitro, polyhalo C_{1-6} alkyl and polyhalo C_{1-6} alkyloxy;

provided that $-X-R^2$ and/or R^3 is other than hydrogen.

20

As used herein C_{1-3} alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 3 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl; C_{1-4} alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as

25 the groups defined for C_{1-3} alkyl and butyl; C_{1-6} alkyl as a group or part of a group

defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-4} alkyl and pentyl, hexyl, 2-methylbutyl and the like; C_{1-10} alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups

30 defined for C_{1-6} alkyl and heptyl, octyl, nonyl, decyl and the like; C_{1-6} alkanediyl as a

group or part of a group defines bivalent straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as methylene, 1,2-ethanediyl or 1,2-ethylidene, 1,3-propanediyl or 1,3-propylidene, 1,4-butanediyl or 1,4-butyldiene and the like; C_{2-6} alkenyl defines straight and branched chain

35 hydrocarbon radicals having from 2 to 6 carbon atoms containing a double bond such

as ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like; C_{2-10} alkenyl defines straight and branched chain hydrocarbon radicals having from 2 to 10 carbon atoms

containing a double bond such as the groups defined for C₂₋₆alkenyl and heptenyl, octenyl, nonenyl, decenyl and the like; C₂₋₆alkenediyl defines bivalent straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing one or more double bonds such as ethenediyl, propenediyl, butenediyl, pentenediyl, 5 hexenediyl and the like; C₂₋₆alkynyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a triple bond such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like; C₂₋₁₀alkynyl defines straight and branched chain hydrocarbon radicals having from 2 to 10 carbon atoms containing a triple bond such as the groups defined for C₂₋₆alkynyl and heptynyl, octynyl, nonynyl, 10 decynyl and the like; C₂₋₆alkynediyl defines bivalent straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a triple bond such as ethynediyl, propynediyl, butynediyl, pentynediyl, hexynediyl and the like; C₃₋₇cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; a monocyclic, bicyclic or tricyclic saturated carbocycle represents a ring 15 system consisting of 1, 2 or 3 rings, said ring system being composed of only carbon atoms and said ring system containing only single bonds; a monocyclic, bicyclic or tricyclic partially saturated carbocycle represents a ring system consisting of 1, 2 or 3 rings, said ring system being composed of only carbon atoms and comprising at least one double bond provided that the ring system is not an aromatic ring system; a 20 monocyclic, bicyclic or tricyclic aromatic carbocycle represents an aromatic ring system consisting of 1, 2 or 3 rings, said ring system being composed of only carbon atoms; the term aromatic is well known to a person skilled in the art and designates cyclically conjugated systems of $4n' + 2$ electrons, that is with 6, 10, 14 etc. π -electrons (rule of Hückel; n' being 1, 2, 3 etc.); a monocyclic, bicyclic or tricyclic saturated 25 heterocycle represents a ring system consisting of 1, 2 or 3 rings and comprising at least one heteroatom selected from O, N or S, said ring system containing only single bonds; a monocyclic, bicyclic or tricyclic partially saturated heterocycle represents a ring system consisting of 1, 2 or 3 rings and comprising at least one heteroatom selected from O, N or S, and at least one double bond provided that the ring system is 30 not an aromatic ring system; a monocyclic, bicyclic or tricyclic aromatic heterocycle represents an aromatic ring system consisting of 1, 2 or 3 rings and comprising at least one heteroatom selected from O, N or S.

Particular examples of monocyclic, bicyclic or tricyclic saturated carbocycles are 35 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[4,2,0]octanyl, cyclononanyl, cyclodecanyl, decahydronaphthalenyl, tetradecahydroanthracenyl.

Particular examples of monocyclic, bicyclic or tricyclic partially saturated carbocycles are cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclo-octenyl, bicyclo[4,2,0]octenyl, cyclononenyl, cyclodecenyl, octahydronaphthalenyl,
5 1,2,3,4-tetrahydronaphthalenyl, 1,2,3,4,4a,9,9a,10-octahydro-anthracenyl.

Particular examples of monocyclic, bicyclic or tricyclic aromatic carbocycles are phenyl, naphthalenyl, anthracenyl.

10 Particular examples of monocyclic, bicyclic or tricyclic saturated heterocycles are tetrahydrofuranyl, pyrrolidinyl, dioxolanyl, imidazolidinyl, thiazolidinyl, tetrahydrothienyl, dihydrooxazolyl, isothiazolidinyl, isoxazolidinyl, oxadiazolidinyl, triazolidinyl, thiadiazolidinyl, pyrazolidinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyrazinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl,
15 trithianyl, decahydroquinolinyl, octahydroindolyl.

Particular examples of monocyclic, bicyclic or tricyclic partially saturated heterocycles are pyrrolinyl, imidazolyl, pyrazolyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, indolyl and the like.

20 Particular examples of monocyclic, bicyclic or tricyclic aromatic heterocycles are azetyl, oxetylidenyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, pyranyl, benzofuryl, isobenzofuryl,
25 benzothienyl, isobenzothienyl, indoliziny, indolyl, isoindolyl, benzoxazolyl, benzimidazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, benzopyrazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoliziny, phthalazinyl, quinoxaliny, quinazoliny, naphthiridinyl, pteridinyl, benzopyranyl, pyrrolopyridyl, thienopyridyl, furopyridyl, isothiazolopyridyl,
30 thiazolopyridyl, isoxazolopyridyl, oxazolopyridyl, pyrazolopyridyl, imidazopyridyl, pyrrolopyrazinyl, thienopyrazinyl, furopyrazinyl, isothiazolopyrazinyl, thiazolopyrazinyl, isoxazolopyrazinyl, oxazolopyrazinyl, pyrazolopyrazinyl, imidazopyrazinyl, pyrrolopyrimidinyl, thienopyrimidinyl, fuopyrimidinyl, isothiazolopyrimidinyl, thiazolopyrimidinyl, isoxazolopyrimidinyl,
35 oxazolopyrimidinyl, pyrazolopyrimidinyl, imidazopyrimidinyl, pyrrolopyridazinyl, thienopyridazinyl, fuopyridazinyl, isothiazolopyridazinyl, thiazolopyridazinyl, isoxazolopyridazinyl, oxazolopyridazinyl, pyrazolopyridazinyl, imidazopyridazinyl,

oxadiazolopyridyl, thiadiazolopyridyl, triazolopyridyl, oxadiazolopyrazinyl, thiadiazolopyrazinyl, triazolopyrazinyl, oxadiazolopyrimidinyl, thiadiazolopyrimidinyl, triazolopyrimidinyl, oxadiazolopyridazinyl, thiadiazolopyridazinyl, triazolopyridazinyl, imidazooxazolyl, imidazothiazolyl, imidazoimidazolyl, isoxazolotriazinyl, isothiazolo-
5 triazinyl, pyrazolotriazinyl, oxazolotriazinyl, thiazolotriazinyl, imidazotriazinyl, oxadiazolotriazinyl, thiadiazolotriazinyl, triazolotriazinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a
10 carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhalomethyl as a group or part of a group is defined as mono- or
15 polyhalosubstituted methyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl; polyhaloC₁₋₆alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C₁₋₆alkyl, for example, the groups defined in halomethyl, 1,1-difluoro-ethyl and the like. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhalomethyl or
20 polyhaloC₁₋₆alkyl, they may be the same or different.

The term heterocycle as in the definition of for instance R², R⁵, R⁶, R⁸ or R¹⁵ is meant to include all the possible isomeric forms of the heterocycles, for instance, pyrrolyl also includes 2H-pyrrolyl.

25

The hereinabove-mentioned carbocycles may be attached to the remainder of the molecule of formula (I) or (I') through any ring carbon as appropriate, if not otherwise specified. Thus, for example, when the partially saturated bicyclic carbocycle is 1,2,3,4-tetrahydronaphthalenyl, it may be 1,2,3,4-tetrahydronaphthalen-1-yl,
30 1,2,3,4-tetrahydronaphthalen-2-yl and the like.

The hereinabove-mentioned heterocycles may be attached to the remainder of the molecule of formula (I) or (I') through any ring carbon or heteroatom as appropriate, if not otherwise specified. Thus, for example, when the aromatic monocyclic heterocycle
35 is imidazolyl, it may be 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and the like.

When any variable (eg. R⁵, R⁶ etc.) occurs more than one time in any constituent, each definition is independent.

5 Lines drawn into ring systems from substituents indicate that the bond may be attached to any of the suitable ring atoms.

For therapeutic use, salts of the compounds of formula (I) or (I') are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or
10 purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to
15 comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) or (I') are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic,
20 propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base
25 form.

The compounds of formula (I) or (I') containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for
30 example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine,
35 di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline, the benzathine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine

salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) or (I') are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) or (I') are able to form by reaction between a basic nitrogen of a compound of formula (I) or (I') and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

It will be appreciated that some of the compounds of formula (I) or (I') and their N-oxides, addition salts, quaternary amines and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I) or (I'), and their N-oxides, addition salts, quaternary amines or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I) or (I') and their N-oxides, salts, solvates or quaternary amines substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other isomers. In particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of formula (I) or (I') are obviously intended to be embraced within the scope of this invention.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several tertiary nitrogen atoms are oxidized to the so-called *N*-oxide.

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Some of the compounds of formula (I) or (I') may also exist in their tautomeric form (e.g. keto-enol tautomerie). Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

- 10 Whenever used hereinafter, the term "compounds of formula (I)" or "compounds of formula (I) or (I') is meant to also include their *N*-oxide forms, their salts, their quaternary amines and their stereochemically isomeric forms. Of special interest are those compounds of formula (I) or (I') which are stereochemically pure.
- 15 Particular compounds are those compounds of formula (I) or (I') as defined hereinabove provided that the molecular mass of the compounds is at most 1000 u, in particular at most 800 u, more in particular at most 700 u (u stands for unified atomic mass unit and equals 1.66×10^{-27} kg).
- 20 Also particular interesting compounds are those compounds of formula (I) or (I') as defined hereinabove, their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms thereof, wherein Z represents O or S;
ring A is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl;
- 25 R^1 is hydrogen; aryl; formyl; C_{1-6} alkylcarbonyl; C_{1-6} alkyl; C_{1-6} alkyloxycarbonyl; C_{1-6} alkyl substituted with formyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylcarbonyloxy; C_{1-6} alkyloxy C_{1-6} alkylcarbonyl optionally substituted with C_{1-6} alkyloxycarbonyl;
- X is $-NR^1$ -; $-NH-NH$ -; $-N=N$ -; $-O$ -; $-C(=O)$ -; $-C(=S)$ -; $-O-C(=O)$ -; $-C(=O)-O$ -;
30 $-O-C(=O)-C_{1-6}alkyl$ -; $-C(=O)-O-C_{1-6}alkyl$ -; $-O-C_{1-6}alkyl-C(=O)$ -;
 $-C(=O)-C_{1-6}alkyl-O$ -; $-O-C(=O)-NR^1$ -; $-NR^1-C(=O)-O$ -; $-O-C(=O)-C(=O)$ -;
 $-C(=O)-NR^1$ -; $-NR^1-C(=O)$ -; $-C(=S)-NR^1$ -; $-NR^1-C(=S)$ -; $-NR^1-C(=O)-NR^1$ -;
 $-NR^1-C(=S)-NR^1$ -; $-NR^1-S(=O)-NR^1$ -; $-NR^1-S(=O)_2-NR^1$ -; $-C_{1-6}alkyl-C(=O)-NR^1$ -;
 $-O-C_{1-6}alkyl-C(=O)-NR^1$ -; $-C_{1-6}alkyl-O-C(=O)-NR^1$ -; $-C_{1-6}alkyl$ -; $-O-C_{1-6}alkyl$ -;
35 $-C_{1-6}alkyl-O$ -; $-NR^1-C_{1-6}alkyl$ -; $-C_{1-6}alkyl-NR^1$ -; $-NR^1-C_{1-6}alkyl-NR^1$ -;
 $-NR^1-C_{1-6}alkyl-C_{3-7}cycloalkyl$ -; $-C_{2-6}alkenyl$ -; $-C_{2-6}alkynyl$ -; $-O-C_{2-6}alkenyl$ -;
 $-C_{2-6}alkenyl-O$ -; $-NR^1-C_{2-6}alkenyl$ -; $-C_{2-6}alkenyl-NR^1$ -; $-NR^1-C_{2-6}alkenyl-NR^1$ -;

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$-\text{NR}^1-\text{C}_{2-6}\text{alkenyl}-\text{C}_{3-7}\text{cycloalkyl}-$; $-\text{O}-\text{C}_{2-6}\text{alkynyl}-$; $-\text{C}_{2-6}\text{alkynyl}-\text{O}-$;
 $-\text{NR}^1-\text{C}_{2-6}\text{alkynyl}-$; $-\text{C}_{2-6}\text{alkynyl}-\text{NR}^1-$; $-\text{NR}^1-\text{C}_{2-6}\text{alkynyl}-\text{NR}^1-$;
 $-\text{NR}^1-\text{C}_{2-6}\text{alkynyl}-\text{C}_{3-7}\text{cycloalkyl}-$; $-\text{O}-\text{C}_{1-6}\text{alkyl}-\text{O}-$; $-\text{O}-\text{C}_{2-6}\text{alkenyl}-\text{O}-$;
 $-\text{O}-\text{C}_{2-6}\text{alkynyl}-\text{O}-$; $-\text{CHOH}-$; $-\text{S}-$; $-\text{S}(=\text{O})-$; $-\text{S}(=\text{O})_2-$; $-\text{S}(=\text{O})-\text{NR}^1-$; $-\text{S}(=\text{O})_2-\text{NR}^1-$;
5 $-\text{NR}^1-\text{S}(=\text{O})-$; $-\text{NR}^1-\text{S}(=\text{O})_2-$; $-\text{S}-\text{C}_{1-6}\text{alkyl}-$; $-\text{C}_{1-6}\text{alkyl}-\text{S}-$; $-\text{S}-\text{C}_{2-6}\text{alkenyl}-$;
 $-\text{C}_{2-6}\text{alkenyl}-\text{S}-$; $-\text{S}-\text{C}_{2-6}\text{alkynyl}-$; $-\text{C}_{2-6}\text{alkynyl}-\text{S}-$; $-\text{O}-\text{C}_{1-6}\text{alkyl}-\text{S}(=\text{O})_2-$ or a direct
bond;

R^2 is hydrogen, $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, R^{20} , each of said groups
representing R^2 may optionally be substituted where possible with one or more
10 substituents each independently being selected from $=\text{S}$; $=\text{O}$; R^{15} ; hydroxy; halo;
nitro; cyano; $\text{R}^{15}-\text{O}-$; SH ; $\text{R}^{15}-\text{S}-$; formyl; carboxyl; $\text{R}^{15}-\text{C}(=\text{O})-$; $\text{R}^{15}-\text{O}-\text{C}(=\text{O})-$;
 $\text{R}^{15}-\text{C}(=\text{O})-\text{O}-$; $\text{R}^{15}-\text{O}-\text{C}(=\text{O})-\text{O}-$; $-\text{SO}_3\text{H}$; $\text{R}^{15}-\text{S}(=\text{O})-$; $\text{R}^{15}-\text{S}(=\text{O})_2-$; $\text{R}^5\text{R}^6\text{N}$;
 $\text{R}^5\text{R}^6\text{N}-\text{C}_{1-6}\text{alkyl}$; $\text{R}^5\text{R}^6\text{N}-\text{C}_{3-7}\text{cycloalkyl}$; $\text{R}^5\text{R}^6\text{N}-\text{C}_{1-6}\text{alkyloxy}$; $\text{R}^5\text{R}^6\text{N}-\text{C}(=\text{O})-$;
 $\text{R}^5\text{R}^6\text{N}-\text{C}(=\text{S})-$; $\text{R}^5\text{R}^6\text{N}-\text{C}(=\text{O})-\text{NH}-$; $\text{R}^5\text{R}^6\text{N}-\text{C}(=\text{S})-\text{NH}-$; $\text{R}^5\text{R}^6\text{N}-\text{S}(=\text{O})_n-$;
15 $\text{R}^5\text{R}^6\text{N}-\text{S}(=\text{O})_n-\text{NH}-$; $\text{R}^{15}-\text{C}(=\text{S})-$; $\text{R}^{15}-\text{C}(=\text{O})-\text{NH}-$; $\text{R}^{15}-\text{O}-\text{C}(=\text{O})-\text{NH}-$;
 $\text{R}^{15}-\text{S}(=\text{O})_n-\text{NH}-$; $\text{R}^{15}-\text{O}-\text{S}(=\text{O})_n-\text{NH}-$; $\text{R}^{15}-\text{C}(=\text{S})-\text{NH}-$; $\text{R}^{15}-\text{O}-\text{C}(=\text{S})-\text{NH}-$;
 $\text{R}^{17}\text{R}^{18}\text{N}-\text{Y}_{1a}-$; $\text{R}^{17}\text{R}^{18}\text{N}-\text{Y}_2-\text{NR}^{16}-\text{Y}_1-$; $\text{R}^{15}-\text{Y}_2-\text{NR}^{19}-\text{Y}_1-$; $\text{H}-\text{Y}_2-\text{NR}^{19}-\text{Y}_1-$;

R^3 is hydrogen; hydroxy; halo; $\text{C}_{1-6}\text{alkyl}$; $\text{C}_{1-6}\text{alkyl}$ substituted with cyano, hydroxy or
 $-\text{C}(=\text{O})\text{R}^7$; $\text{C}_{2-6}\text{alkenyl}$; $\text{C}_{2-6}\text{alkenyl}$ substituted with one or more halogen atoms or
20 cyano; $\text{C}_{2-6}\text{alkynyl}$; $\text{C}_{2-6}\text{alkynyl}$ substituted with one or more halogen atoms or
cyano; $\text{C}_{1-6}\text{alkyloxy}$; $\text{C}_{1-6}\text{alkylthio}$; $\text{C}_{1-6}\text{alkyloxycarbonyl}$; $\text{C}_{1-6}\text{alkylcarbonyloxy}$;
carboxyl; cyano; nitro; amino; mono- or di($\text{C}_{1-6}\text{alkyl}$)amino; polyhalo $\text{C}_{1-6}\text{alkyl}$;
polyhalo $\text{C}_{1-6}\text{alkyloxy}$; polyhalo $\text{C}_{1-6}\text{alkylthio}$; R^{21} ; $\text{R}^{21}-\text{C}_{1-6}\text{alkyl}$; $\text{R}^{21}-\text{O}-$; $\text{R}^{21}-\text{S}-$;
 $\text{R}^{21}-\text{C}(=\text{O})-$; $\text{R}^{21}-\text{S}(=\text{O})_p-$; $\text{R}^7-\text{S}(=\text{O})_p-$; $\text{R}^7-\text{S}(=\text{O})_p-\text{NH}-$; $\text{R}^{21}-\text{S}(=\text{O})_p-\text{NH}-$;
25 $\text{R}^7-\text{C}(=\text{O})-$; $-\text{NHC}(=\text{O})\text{H}$; $-\text{C}(=\text{O})\text{NHNH}_2$; $\text{R}^7-\text{C}(=\text{O})-\text{NH}-$; $\text{R}^{21}-\text{C}(=\text{O})-\text{NH}-$;
 $-\text{C}(=\text{NH})\text{R}^7$; $-\text{C}(=\text{NH})\text{R}^{21}$;

R^{4a} or R^{4b} each independently are hydrogen, R^8 , $-\text{Y}_1-\text{NR}^9-\text{Y}_2-\text{NR}^{10}\text{R}^{11}$, $-\text{Y}_1-\text{NR}^9-\text{Y}_1-\text{R}^8$,
 $-\text{Y}_1-\text{NR}^9\text{R}^{10}$;

R^5 and R^6 each independently are hydrogen, R^8 , $-\text{Y}_1-\text{NR}^9-\text{Y}_2-\text{NR}^{10}\text{R}^{11}$, $-\text{Y}_1-\text{NR}^9-\text{Y}_1-\text{R}^8$,
30 $-\text{Y}_1-\text{NR}^9\text{R}^{10}$;

R^7 is $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyloxy}$, amino, mono- or di($\text{C}_{1-6}\text{alkyl}$)amino or polyhalo $\text{C}_{1-6}\text{alkyl}$;

R^8 is $\text{C}_{1-6}\text{alkyl}$; $\text{C}_{2-6}\text{alkenyl}$; $\text{C}_{2-6}\text{alkynyl}$; a monocyclic, bicyclic or tricyclic saturated
carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a
monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or
35 tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated
heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; $\text{C}_{1-6}\text{alkyl}$
substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a

- monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic, bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic saturated heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of said groups representing R⁸ may optionally be substituted with one or more substituents selected from R¹², R¹³ and R¹⁴;
- R⁹, R¹⁰ and R¹¹ each independently are hydrogen or R⁸;
- R¹², R¹³ and R¹⁴ each independently are hydrogen; R¹⁵; hydroxy; halo; nitro; cyano; R¹⁵-O-; SH; R¹⁵-S-; formyl; carboxyl; R¹⁵-C(=O)-; R¹⁵-O-C(=O)-; R¹⁵-C(=O)-O-; R¹⁵-O-C(=O)-O-; -SO₃H; R¹⁵-S(=O)-; R¹⁵-S(=O)₂-; R¹⁵R¹⁶N-S(=O)-; R¹⁵R¹⁶N-S(=O)₂-; R¹⁷R¹⁸N-Y₁-; R¹⁷R¹⁸N-Y₂-NR¹⁶-Y₁-; R¹⁵-Y₂-NR¹⁹-Y₁-; H-Y₂-NR¹⁹-Y₁-; oxo;
- R¹⁵ is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; C₁₋₆alkyl substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic, bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic saturated heterocycle or with a monocyclic, bicyclic or tricyclic partially saturated heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of said substituents representing R¹⁵ may optionally be substituted with one or more substituents selected from R¹², R¹³ and R¹⁴;
- R¹⁶, R¹⁷, R¹⁸ and R¹⁹ each independently are hydrogen or R¹⁵;
- R²⁰ is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle;
- R²¹ is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle, each of said carbocycles or heterocycles representing R²¹ may optionally be substituted with one or more substituents selected from R¹², R¹³ and R¹⁴;

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Y_{1a} is $-Y_3-S(=O)-Y_4-$; $-Y_3-S(=O)_2-Y_4-$; $-Y_3-C(=O)-Y_4-$; $-Y_3-C(=S)-Y_4-$; $-Y_3-O-Y_4-$,
 $-Y_3-S-Y_4-$; $-Y_3-O-C(=O)-Y_4-$ or $-Y_3-C(=O)-O-Y_4-$;

Y_1 or Y_2 each independently are a direct bond, $-Y_3-S(=O)-Y_4-$; $-Y_3-S(=O)_2-Y_4-$,
 $-Y_3-C(=O)-Y_4-$; $-Y_3-C(=S)-Y_4-$; $-Y_3-O-Y_4-$; $-Y_3-S-Y_4-$; $-Y_3-O-C(=O)-Y_4-$ or
 5 $-Y_3-C(=O)-O-Y_4-$;

Y_3 or Y_4 each independently are a direct bond, C_{1-6} alkanediyl, C_{2-6} alkenediyl or
 C_{2-6} alkynediyl;

n is 1 or 2;

m is 1 or 2;

10 p is 1 or 2;

r is 1 to 5;

s is 1 to 3;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each
 independently selected from halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, cyano,

15 nitro, polyhalo C_{1-6} alkyl and polyhalo C_{1-6} alkyloxy;

provided that $-X-R^2$ and/or R^3 is other than hydrogen; and

provided that the following compounds

N-methoxy-*N*-methyl-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinecarboxamide
 and *N*-phenyl-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinecarboxamide are not

20 included.

Further particular compounds are those compounds of formula (I) or (I') wherein ring
 A is pyrimidinyl, pyrazinyl or pyridazinyl, in particular pyrimidinyl, and wherein R^3 is
 other than C_{1-6} alkyloxy or polyhalo C_{1-6} alkyloxy.

25

Yet further particular compounds are those compounds of formula (I) or (I') wherein
 ring A is pyrimidinyl, pyrazinyl or pyridazinyl, in particular pyrimidinyl;

R^1 is hydrogen; aryl; formyl; C_{1-6} alkylcarbonyl; C_{1-6} alkyl; C_{1-6} alkyloxycarbonyl;

C_{1-6} alkyl substituted with formyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl,

30 C_{1-6} alkylcarbonyloxy; C_{1-6} alkyloxy C_{1-6} alkylcarbonyl optionally substituted with

C_{1-6} alkyloxycarbonyl;

X is $-NR^1-$; $-C(=O)-$; $-O-C(=O)-$; $-C(=O)-O-$; $-O-C(=O)-C_{1-6}$ alkyl-; $-C(=O)-O-$

C_{1-6} alkyl-; $-O-C_{1-6}$ alkyl- $C(=O)-$; $-C(=O)-C_{1-6}$ alkyl- $O-$; $-O-C(=O)-NR^1-$; $-NR^1-$

$C(=O)-O-$; $-C(=O)-NR^1-$; $-NR^1-C(=O)-$; $-C_{1-6}$ alkyl-; $-O-C_{1-6}$ alkyl-; $-C_{1-6}$ alkyl- $O-$;

35 $-NR^1-C_{1-6}$ alkyl-; $-C_{1-6}$ alkyl- NR^1- ; $-NR^1-C_{1-6}$ alkyl- NR^1- ; $-C_{2-6}$ alkenyl-; $-C_{2-6}$ alkynyl-;

$-O-C_{2-6}$ alkenyl-; $-C_{2-6}$ alkenyl- $O-$; $-NR^1-C_{2-6}$ alkenyl-; $-C_{2-6}$ alkenyl- NR^1- ;

$-NR^1-C_{2-6}$ alkynyl- NR^1- ; $-O-C_{2-6}$ alkynyl-; $-C_{2-6}$ alkynyl- $O-$; $-NR^1-C_{2-6}$ alkynyl-;

- C₂₋₆alkynyl-NR¹-; -NR¹-C₂₋₆alkynyl-NR¹-; -O-C₁₋₆alkyl-O-; -O-C₂₋₆alkenyl-O-;
 -O-C₂₋₆alkynyl-O-; -CHOH-; -S(=O)-; -S(=O)₂-; -S(=O)-NR¹-; -S(=O)₂-NR¹-;
 -NR¹-S(=O)-; -NR¹-S(=O)₂-; -S-C₁₋₆alkyl-; -C₁₋₆alkyl-S-; -S-C₂₋₆alkenyl-;
 -C₂₋₆alkenyl-S-; -S-C₂₋₆alkynyl-; -C₂₋₆alkynyl-S-;
- 5 R² is hydrogen, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, R²⁰, each of said groups
 representing R² may optionally be substituted where possible with one or more
 substituents each independently being selected from =O; R¹⁵; hydroxy; halo; nitro;
 cyano; R¹⁵-O-; SH; R¹⁵-S-; formyl; carboxyl; R¹⁵-C(=O)-; R¹⁵-O-C(=O)-;
 R¹⁵-C(=O)-O-; R¹⁵-O-C(=O)-O-; -SO₃H; R¹⁵-S(=O)-; R¹⁵-S(=O)₂-; R⁵R⁶N;
 10 R⁵R⁶N-C₁₋₆alkyl; R⁵R⁶N-C₁₋₆alkyloxy; R⁵R⁶N-C(=O)-; R⁵R⁶N-S(=O)_n-; R⁵R⁶N-
 S(=O)_n-NH-; R¹⁵-C(=O)-NH-;
- R³ is hydroxy; halo; C₁₋₆alkyl substituted with cyano, hydroxy or -C(=O)R⁷;
 C₂₋₆alkenyl; C₂₋₆alkenyl substituted with one or more halogen atoms or cyano;
 C₂₋₆alkynyl; C₂₋₆alkynyl substituted with one or more halogen atoms or cyano;
- 15 C₁₋₆alkylthio; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxy; carboxyl; cyano; nitro;
 amino; mono- or di(C₁₋₆alkyl)amino; polyhaloC₁₋₆alkyl; polyhaloC₁₋₆alkylthio; R²¹;
 R²¹-C₁₋₆alkyl; R²¹-O-; R²¹-S-; R²¹-C(=O)-; R²¹-S(=O)_p-; R⁷-S(=O)_p-; R⁷-C(=O)-;
 -NHC(=O)H; -C(=O)NHNH₂; R⁷-C(=O)-NH-; R²¹-C(=O)-NH-; -C(=NH)R⁷;
 -C(=NH)R²¹;
- 20 R^{4a} or R^{4b} each independently are hydrogen or R⁸;
 R⁵ and R⁶ each independently are hydrogen or R⁸;
 R⁷ is C₁₋₆alkyl, C₁₋₆alkyloxy, amino, mono- or di(C₁₋₆alkyl)amino or polyhaloC₁₋₆alkyl;
 R⁸ is C₁₋₆alkyl; C₂₋₆alkenyl; C₂₋₆alkynyl; a monocyclic, bicyclic or tricyclic saturated
 carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a
 25 monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or
 tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated
 heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; C₁₋₆alkyl
 substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a
 monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic,
 30 bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic
 saturated heterocycle or with a monocyclic, bicyclic or tricyclic partially saturated
 heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle;
- R¹², R¹³ and R¹⁴ each independently are hydrogen; R¹⁵; hydroxy; halo; nitro; cyano;
 R¹⁵-O-; SH; R¹⁵-S-; formyl; carboxyl; R¹⁵-C(=O)-; R¹⁵-O-C(=O)-; R¹⁵-C(=O)-O-;
 35 R¹⁵-O-C(=O)-O-; -SO₃H; R¹⁵-S(=O)-; R¹⁵-S(=O)₂-; R¹⁵R¹⁶N-S(=O)-;
 R¹⁵R¹⁶N-S(=O)₂-;

R¹⁵ is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; C₁₋₆alkyl substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic, bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic saturated heterocycle or with a monocyclic, bicyclic or tricyclic partially saturated heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of said substituents representing R¹⁵ may optionally be substituted with one or more substituents selected from R¹², R¹³ and R¹⁴;

R¹⁶ is hydrogen or R¹⁵;

R²⁰ is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle;

R²¹ is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle, each of said carbocycles or heterocycles representing R²¹ may optionally be substituted with one or more substituents selected from R¹², R¹³ and R¹⁴;

n is 1 or 2;

m is 1 or 2;

p is 1 or 2;

s is 1 to 3;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy.

Further interesting compounds are those compounds of formula (I) or (I') as defined hereinabove wherein

Z represents O;

ring A is pyridyl or pyrimidinyl;

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R^1 is hydrogen;

X is -O-, -O-C(=O)-NR¹-; -O-C₁₋₆alkyl-; -O-C₂₋₆alkenyl-; -O-C₁₋₆alkyl-O- or a direct bond;

R^2 is hydrogen, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, R^{20} , each of said groups representing R^2 may optionally be substituted where possible with one or more substituents each independently being selected from R^{15} ; halo; nitro; cyano; R^{15} -O-; R^5R^6N ; $R^5R^6N-S(=O)_n-NH$ -;

R^3 is hydrogen or cyano;

R^{4a} or R^{4b} each independently are hydrogen or R^8 ;

R^5 and R^6 each independently are hydrogen or R^8 ;

R^8 is C₁₋₆alkyl;

R^{12} , R^{13} and R^{14} each independently are hydrogen; R^{15} ; halo; nitro; cyano;

$R^{17}R^{18}N-Y_1$;

R^{15} is C₁₋₆alkyl, a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of said substituents representing R^{15} may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;

R^{18} and R^{19} are hydrogen;

R^{20} is a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle;

Y_1 is a direct bond;

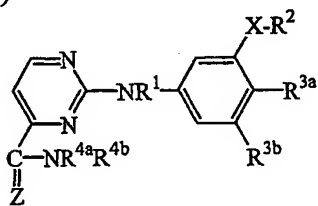
n is 1 or 2;

s is 1;

provided that -X- R^2 and/or R^3 is other than hydrogen.

Yet further interesting compounds are those compounds of formula (I) or (I') as defined hereinabove provided that the compound is other than

a)



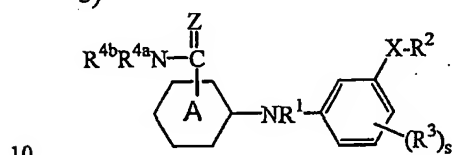
wherein

Z is as defined hereinabove; X is O; R^2 is C₁₋₁₀alkyl, C₂₋₁₀alkenyl or C₂₋₁₀alkynyl, said groups representing R^2 may optionally be substituted; R^{3a} is C₁₋₆alkyloxy; R^{3b} is

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hydrogen, halo, optionally substituted C₁₋₁₀alkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₂₋₁₀alkynyl, hydroxy, amino, mono -or di(C₁₋₆alkyl)amino, C₁₋₆alkyl-C(=O)-NH-, C₁₋₆alkyloxy, polyhaloC₁₋₆alkyloxy, C₁₋₆alkylthio, polyhaloC₁₋₆alkylthio, aryloxy; R¹ is hydrogen or C₁₋₆alkyl; R^{4a} and R^{4b} are each
 5 independently hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkenyl, C₃₋₁₀heterocycloalkyl, C₃₋₁₀heterocycloalkenyl, a C₆₋₁₄aromatic group, a C₅₋₁₄ heteroaromatic group, each of said groups representing R^{4a} and R^{4b} may optionally be substituted;

b)



wherein Z, ring A, R^{4a} and R^{4b}, R², R³ and s are as defined hereinabove; R¹ is hydrogen; aryl; C₁₋₆alkylcarbonyl; C₁₋₆alkyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylcarbonyloxy; C₁₋₆alkyloxyC₁₋₆alkylcarbonyl optionally substituted with
 15 C₁₋₆alkyloxycarbonyl; X is a direct bond or C₁₋₆alkyl.

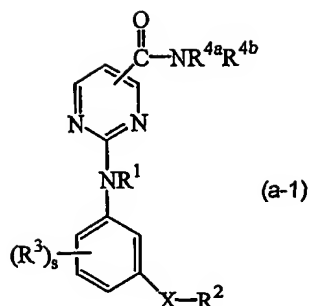
Further preferred compounds are those compounds of formula (I) or (I') wherein one or where possible more of the following restrictions apply :

- a) X is a direct bond and R² is hydrogen;
- 20 b) R² and R³ are other than hydrogen;
- c) R³ is hydrogen;
- d) when s is 1 and said R³ substituent is placed at the para position compared to the NR¹ linker then said R³ substituent is other than C₁₋₆alkyloxy or polyhaloC₁₋₆alkyloxy;
- e) X is other than a direct bond or C₁₋₆alkyl;
- 25 f) both X-R² and R³ are other than hydrogen.

Also preferred are those compounds of formula (I) or (I') wherein the compounds are compounds selected from one of the following formulae :

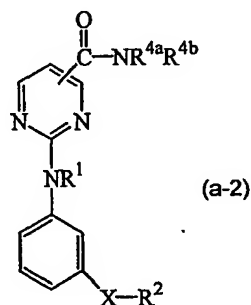
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1)

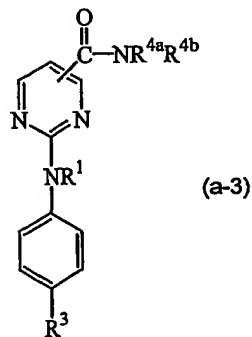


- wherein R^3 is suitably hydrogen; hydroxy; halo; C_{1-6} alkyl; C_{1-6} alkyl substituted with cyano, hydroxy or $-C(=O)R^7$; C_{2-6} alkenyl; C_{2-6} alkenyl substituted with one or more halogen atoms or cyano; C_{2-6} alkynyl; C_{2-6} alkynyl substituted with one or more halogen atoms or cyano; C_{1-6} alkylthio; C_{1-6} alkyloxycarbonyl; C_{1-6} alkylcarbonyloxy; carboxyl; cyano; nitro; amino; mono- or di(C_{1-6} alkyl)amino; polyhalo C_{1-6} alkyl; polyhalo C_{1-6} alkylthio; R^{21} ; $R^{21}-C_{1-6}$ alkyl; $R^{21}-O-$; $R^{21}-S-$; $R^{21}-C(=O)-$; $R^{21}-S(=O)_p-$; $R^7-S(=O)_p-$; $R^7-S(=O)_p-NH-$; $R^{21}-S(=O)_p-NH-$; $R^7-C(=O)-$; $-NHC(=O)H$;
 10 $-C(=O)NHNH_2$; $R^7-C(=O)-NH-$; $R^{21}-C(=O)-NH-$; $-C(=NH)R^7$; $-C(=NH)R^{21}$;

2)



3)



15

Also preferred are those compounds of formula (a-1) wherein one or more, preferably all of the following restrictions apply

(a) s is 1 and said R^3 substituent is placed at the para position compared to the NR^1 linker;

(b) X is other than a direct bond or C_{1-6} alkyl.

5 Particular preferred compounds of formula (I) or (I') are those compounds selected from

2-[[4-cyano-3-[[[(dimethylamino)sulfonyl]amino]phenyl]methoxy]phenyl]amino]-4-pyrimidinecarboxamide (compound 8);

2-[[4-cyano-3-[(2-quinolinylmethoxy)phenyl]amino]-4-pyrimidinecarboxamide
10 (compound 21);

2-[[4-cyano-3-[2-(4-fluorophenoxy)propoxy]phenyl]amino]-4-pyrimidinecarboxamide (compound 16);

2-[[4-cyano-3-[(2-methoxyphenyl)methoxy]phenyl]amino]-4-pyrimidinecarboxamide compound 30);

15 2-[[4-cyano-3-[(1-ethyl-1*H*-imidazol-2-yl)methoxy]phenyl]amino]-4-pyrimidinecarboxamide compound 24);

2-[[4-cyano-3-(phenylmethoxy)phenyl]amino]-4-pyrimidinecarboxamide (compound 2);

2-[[4-cyano-3-[(4-methoxyphenyl)methoxy]phenyl]amino]-4-pyrimidinecarboxamide
20 (compound 13);

2-[[4-cyano-3-(2-naphthalenylmethoxy)phenyl]amino]-4-pyrimidinecarboxamide (compound 38);

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

25

Other particular preferred compounds of formula (I) or (I') are those compounds selected from

2-(3-benzyloxy-4-cyano-phenylamino)-nicotinamide;

6-(3-benzyloxy-4-cyano-phenylamino)-nicotinamide;

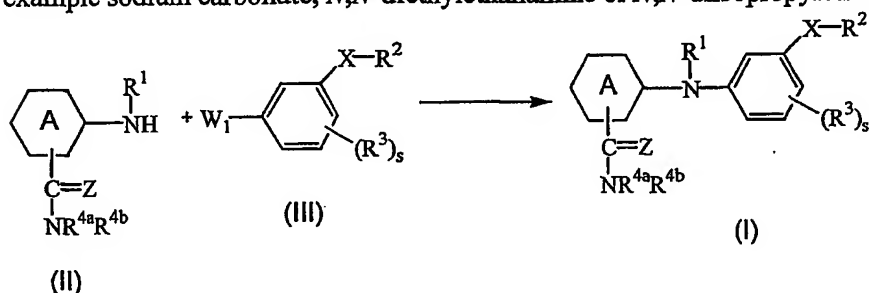
30 4-(3-benzyloxy-4-cyano-phenylamino)-pyridine-2-carboxylic acid amide;

2-(3-benzyloxy-4-cyano-phenylamino)-isonicotinamide;

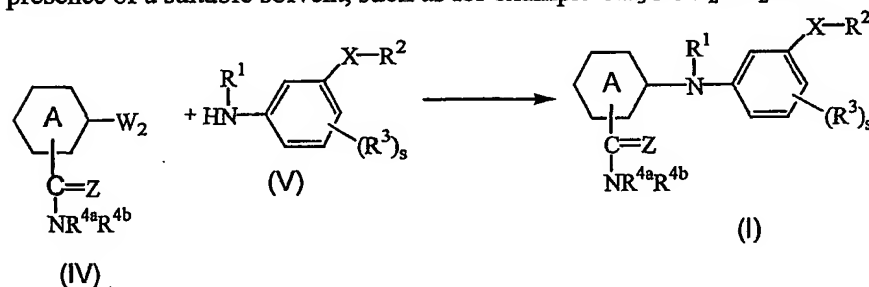
a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

35 Compounds of formula (I) can be prepared by reacting an intermediate of formula (II) with an intermediate of formula (III) wherein W_1 represents a suitable leaving group, such as for example a halo atom, e.g. chloro, bromo, or C_{1-6} alkyl-S-, in the presence of

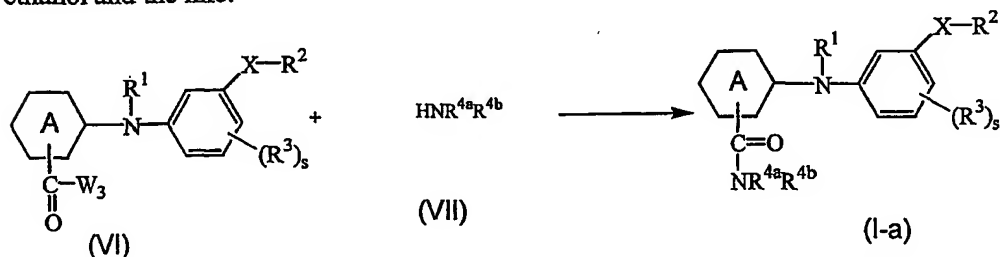
a suitable solvent, such as for example *N,N*-dimethylacetamide, *N,N*-dimethylformamide, methylene chloride, $(\text{CH}_3\text{OCH}_2\text{CH}_2)_2\text{O}$, tetrahydrofuran, water, an alcohol, e.g. ethanol, isopropanol and the like, and optionally in the presence of a suitable acid, such as for example hydrochloric acid, or a suitable base, such as for example sodium carbonate, *N,N*-diethylethanamine or *N,N*-diisopropylethanamine.



Compounds of formula (I) can also be prepared by reacting an intermediate of formula (IV) wherein W_2 represents a suitable leaving group, such as for example a halo atom, e.g. chloro, bromo and the like, with an intermediate of formula (V) optionally in the presence of a suitable solvent, such as for example $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$.



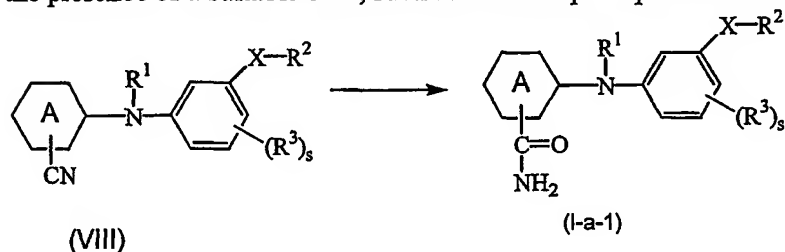
Compounds of formula (I) wherein Z is O, said compounds being represented by formula (I-a), can be prepared by reacting an intermediate of formula (VI) wherein W_3 represents a suitable leaving group, such as for example a halo atom, e.g. chloro, bromo and the like, or C_{1-6} alkyloxy, with an intermediate of formula (VII) in the presence of a suitable solvent, such as for example tetrahydrofuran or an alcohol, e.g. methanol, ethanol and the like.



Compounds of formula (I) wherein Z is O and R^{4a} and R^{4b} are hydrogen, said compounds being represented by formula (I-a-1), can be prepared by reacting an intermediate of formula (VIII) with a suitable oxidizing agent, such as for example

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H₂O₂ or NaBO₃, in the presence of a suitable solvent, such as for example water, dimethylsulfoxide or an alcohol, e.g. methanol, ethanol and the like, and optionally in the presence of a suitable base, such as for example dipotassium carbonate.



- 5 In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

- 10 The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions.

- The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboxy-
 15 peroxy acid or halo substituted benzenecarboxy-
 peroxy acid, e.g. 3-chlorobenzenecarboxy-
 peroxy acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. t-butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

25

- Compounds of formula (I) wherein R³ is halo, or wherein R² is substituted with halo, can be converted into a compound of formula (I) wherein R³ is cyano, or wherein R² is substituted with cyano, by reaction with a suitable cyano-introducing agent, such as sodium cyanide or CuCN, optionally in the presence of a suitable catalyst, such as for
 30 example tetrakis(triphenylphosphine)palladium and a suitable solvent, such as *N,N*-dimethylacetamide or *N,N*-dimethylformamide. A compound of formula (I) wherein R³ is cyano, or wherein R² is substituted with cyano, can further be converted

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into a compound of formula (I) wherein R^3 is aminocarbonyl, or wherein R^2 is substituted with aminocarbonyl, by reaction with $HCOOH$, in the presence of a suitable acid, such as hydrochloric acid. A compound of formula (I) wherein R^3 is cyano, or wherein R^2 is substituted with cyano, can also further be converted into a compound of formula (I) wherein R^3 is tetrazolyl, or wherein R^2 is substituted with tetrazolyl, by
5 reaction with sodium azide in the presence of ammonium chloride and *N, N*-dimethylacetoacetamide.

Compounds of formula (I) wherein R^2 is substituted with halo can also be converted
10 into a compound of formula (I) wherein R^2 is substituted with mercapto, by reaction with disodium sulfide in the presence of a suitable solvent, such as, for example, 1,4-dioxane.

Compounds of formula (I) wherein R^2 is substituted with halo, can also be converted
15 into a compound of formula (I) wherein R^2 is substituted with C_{1-6} alkylthio, by reaction with a reagent of formula alkaline metal⁺ $^-S-C_{1-6}$ alkyl, e.g. $Na^+ ^-S-C_{1-6}$ alkyl, in the presence of a suitable solvent, such as dimethylsulfoxide. The latter compounds can further be converted into a compound of formula (I) wherein R^2 is substituted with C_{1-6} alkyl-S(=O)-, by reaction with a suitable oxidizing agent, such as a peroxide, e.g.
20 3-chlorobenzenecarboxoperoxoic acid, in the presence of a suitable solvent, such as an alcohol, e.g. ethanol.

Compounds of formula (I) wherein R^3 is halo, or wherein R^2 is substituted with halo, can also be converted into a compound of formula (I) wherein R^3 is C_{1-6} alkyloxy, or
25 wherein R^2 is substituted with C_{1-6} alkyloxy, by reaction with an alcoholate salt, such as, for example, $LiOC_{1-6}$ alkyl, in the presence of a suitable solvent, such as an alcohol, e.g. methanol.

Compounds of formula (I) wherein R^3 is halo, or wherein R^2 is substituted with halo, can also be converted into a compound of formula (I) wherein R^3 is hydroxy, or
30 wherein R^2 is substituted with hydroxy, by reaction with a suitable carboxylate, e.g. sodium acetate, in a suitable reaction-inert solvent, such as, for example, dimethylsulfoxide, followed by treating the obtained reaction product with a suitable base, such as pyridine, and acetyl chloride.

35 Compounds of formula (I) wherein R^3 is halo, or wherein R^2 is substituted with halo, can also be converted into a compound of formula (I) wherein R^3 is a monocyclic,

- bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle, or wherein R^2 is substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle, said substituents being represented by -L, by reaction with H-L in the presence of a suitable base, such as for example sodium hydroxide, dipotassium carbonate, sodium hydride, in the presence of a suitable solvent, such as, for example, 1,4-dioxane, *N,N*-dimethylacetamide, *N,N*-dimethylformamide.
- 15 Compounds of formula (I) wherein R^3 is chloro, or wherein R^2 is substituted with chloro, can be converted into a compound of formula (I) wherein R^3 is fluoro, or wherein R^2 is substituted with fluoro, by reaction with a suitable fluoride salt, such as for example potassium fluoride, in the presence of a suitable solvent, e.g. sulfolane.
- 20 Compounds of formula (I) wherein $X-R^2$ is hydrogen and wherein the R^3 substituent positioned at the meta position compared to the NR^1 linker, is halo, can be converted into a compound of formula (I) wherein said R^3 substituent is replaced by $X-R^2$ wherein X is other than a direct bond when R^2 is hydrogen, by reaction with $H-X-R^2$ in the presence of a suitable solvent, such as *N,N*-dimethylacetamide or
- 25 *N,N*-dimethylformamide optionally in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine.
- Compounds of formula (I) wherein R^2 is substituted with C_{1-6} alkyloxy C_{1-6} alkyl, can be converted into a compound of formula (I) wherein R^2 is substituted with
- 30 hydroxy C_{1-6} alkyl, by dealkylating the ether in the presence of a suitable dealkylating agent, such as, for example, tribromoborane, and a suitable solvent, such as methylene chloride.
- Compounds of formula (I) wherein R^3 or $X-R^2$ are C_{1-6} alkyloxycarbonyl, or wherein R^2 is substituted with C_{1-6} alkyloxycarbonyl, can be converted into a compound of formula (I) wherein R^3 or $X-R^2$ are aminocarbonyl, or wherein R^2 is substituted with aminocarbonyl or mono- or di(C_{1-6} alkyl)aminocarbonyl by reaction with a suitable

agent such as ammonia, $\text{NH}_2(\text{C}_{1-6}\text{alkyl})$, $\text{AlCH}_3[\text{N}(\text{C}_{1-6}\text{alkyl})_2]\text{Cl}$ optionally in the presence of a suitable acid, such as for example hydrochloric acid, and in the presence of a suitable solvent such as an alcohol, e.g. methanol; tetrahydrofuran; *N,N*-diisopropylethane.

5

Compounds of formula (I) wherein R^3 is hydrogen or wherein R^2 is unsubstituted, can be converted into a compound wherein R^3 is halo or wherein R^2 is substituted with halo, by reaction with a suitable halogenating agent, such as, for example Br_2 or 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis[tetrafluoroborate], in the presence of a suitable solvent, such as tetrahydrofuran, water, acetonitrile, chloroform and optionally in the presence of a suitable base such as *N,N*-diethylethanamine.

10

Compounds of formula (I) wherein R^3 or $-\text{X}-\text{R}^2$ are C_{1-6} alkyloxycarbonyl or wherein R^2 is substituted with C_{1-6} alkyloxycarbonyl, can be converted into a compound of formula (I) wherein R^3 or $\text{X}-\text{R}^2$ are hydroxymethyl or wherein R^2 is substituted with hydroxymethyl by reaction with a suitable reducing agent, such as for example LiAlH_4 .

15

Compounds of formula (I) wherein $-\text{X}-\text{R}^2$ is $-\text{O}-\text{CH}_2$ -(optionally substituted)phenyl may be converted into a compound of formula (I) wherein $-\text{X}-\text{R}^2$ represents OH by reaction with a suitable reducing agent, such as H_2 , in the presence of a suitable catalyst, such as for example palladium on charcoal, and a suitable solvent, such as for example an alcohol, e.g. methanol, ethanol and the like, or *N,N*-dimethylacetamide. Compounds of formula (I) wherein $-\text{X}-\text{R}^2$ represents OH may be converted into a compound of formula (I) wherein $-\text{X}-\text{R}^2$ represents $-\text{O}-\text{X}_1-\text{R}^2$ by reaction with $\text{W}_1-\text{X}_1-\text{R}^2$ wherein W_1 represents a suitable leaving group, such as for example a halo atom, e.g. chloro, and wherein $-\text{O}-\text{X}_1$ represents those linkers falling under the definition of X which are attached to the phenyl ring via a O atom (in said definition X_1 represents that part of the linker wherein the O atom is not included), in the presence of a suitable base, such as for example dipotassium carbonate, and a suitable solvent, such as for example *N,N*-dimethylacetamide.

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Compounds of formula (I) wherein R^3 is nitro, or wherein R^2 is substituted with nitro, may be converted into a compound of formula (I) wherein R^3 is amino or wherein R^2 is substituted with amino, by reaction with a suitable reducing agent, such as for example H_2 , in the presence of a suitable catalyst, such as for example palladium on charcoal, a

35

suitable catalyst poison, such as for example a thiophene solution, and a suitable solvent, such as for example an alcohol, e.g. methanol, ethanol and the like.

5 Compounds of formula (I) wherein R^2 is substituted with NH_2 , can be converted into a compound of formula (I) wherein R^2 is substituted with $NH-S(=O)_2-NR^5R^6$, by reaction with $W_1-S(=O)_2-NR^5R^6$ wherein W_1 represents a suitable leaving group such as for example a halo atom, e.g. chloro, in the presence of a suitable solvent, such as for example *N,N*-dimethylacetamide and a suitable base, such as for example *N,N*-diethylethanamine.

10 Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical
15 methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or
20 compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the
25 intervening reactions occur stereospecifically.

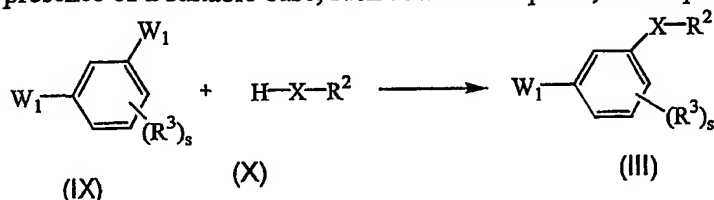
An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

30 Some of the intermediates and starting materials are known compounds and may be commercially available or may be prepared according to art-known procedures, such as those described in WO 99/50250, WO 00/27825 or EP 0,834,507.

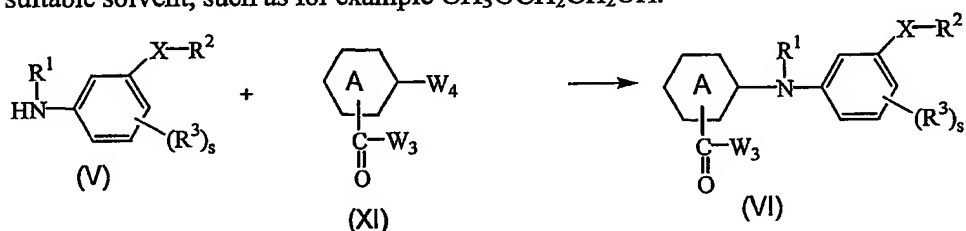
35 Intermediates of formula (III) can be prepared by reacting an intermediate of formula (IX) wherein W_1 is as defined hereinabove, with an intermediate of formula (X) in the

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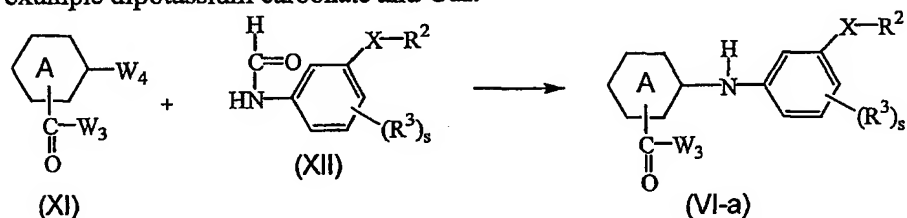
presence of a suitable solvent, such as for example acetonitrile or dioxane, and in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine.



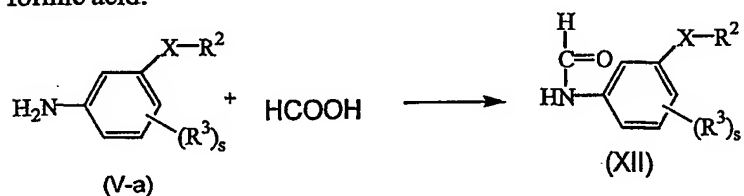
- Intermediates of formula (VI) can be prepared by reacting an intermediate of formula (V) with an intermediate of formula (XI) wherein W_4 represents a suitable leaving group, such as for example a halo atom, e.g. chloro and the like, in the presence of a suitable solvent, such as for example $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$.



- Intermediates of formula (VI) wherein R^1 is hydrogen, said intermediates being represented by formula (VI-a), can be prepared by reacting an intermediate of formula (XI) with an intermediate of formula (XII) in the presence of a suitable salt such as for example dipotassium carbonate and CuI .

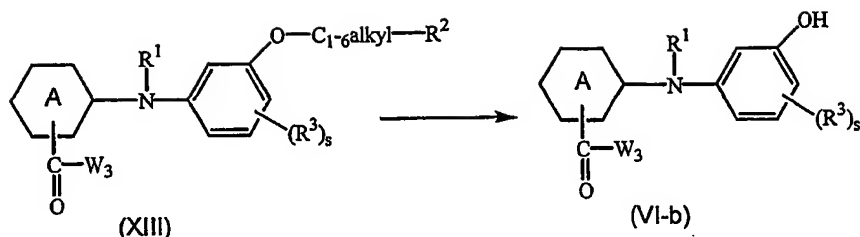


- Intermediates of formula (XII) can be prepared by reacting an intermediate of formula (V) wherein R^1 is hydrogen, said intermediate being represented by formula (V-a), with formic acid.

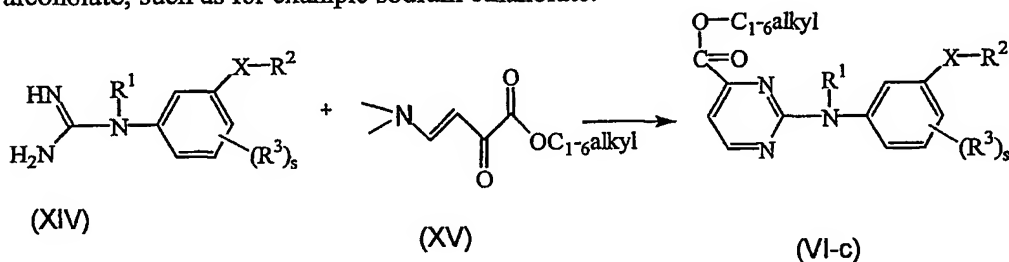


- Intermediates of formula (VI) wherein X-R^2 is OH , said intermediates being represented by formula (VI-b), can be prepared by reducing an intermediate of formula (XIII) in the presence of a suitable reducing agent, such as for example H_2 , a suitable catalyst, such as palladium on charcoal, and a suitable solvent, such as an alcohol, e.g. ethanol and the like.

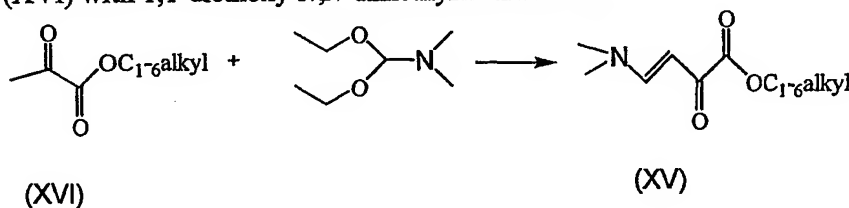
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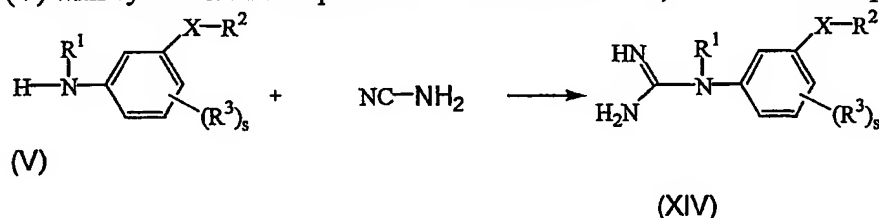
Intermediates of formula (VI) wherein ring A is pyrimidine with the NR^1 linker in position 2 and W_3 represents an alcoholate, i.e. $\text{C}_{1-6}\text{alkylO}-$, said intermediates being represented by formula (VI-c), can be prepared by reacting an intermediate of formula (XIV) with an intermediate of formula (XV) in the presence of a suitable solvent, such as for example *N,N*-dimethylacetamide, optionally in the presence of a suitable alcoholate, such as for example sodium ethanolate.



Intermediates of formula (XV) can be prepared by reacting an intermediate of formula (XVI) with 1,1-diethoxy-*N,N*-dimethylmethanamine.

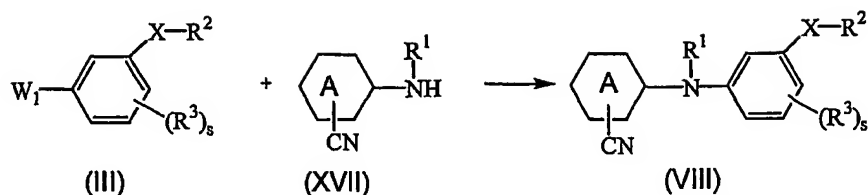


Intermediates of formula (XIV) can be prepared by reacting an intermediate of formula (V) with cyanamide in the presence of a suitable solvent, such as for example diglyme.

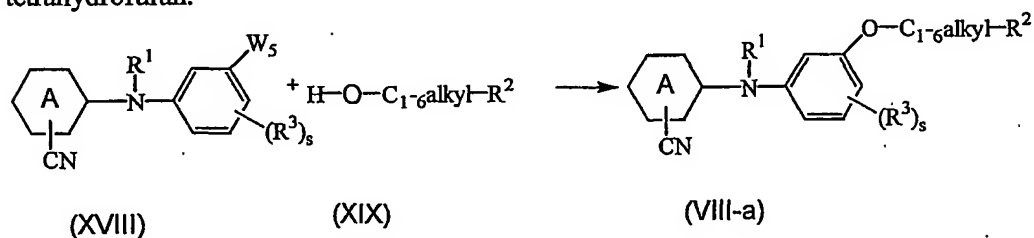


Intermediates of formula (VIII) can be prepared by reacting an intermediate of formula (III) with an intermediate of formula (XVII) in the presence of a suitable solvent, such as for example dioxane and diethylether, and a suitable acid, such as for example hydrochloric acid.

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Intermediates of formula (VIII) wherein X is $-O-C_{1-6}alkyl$, said intermediates being represented by formula (VIII-a), can be prepared by reacting an intermediate of formula (XVIII) wherein W_5 represents a suitable leaving group such as for example a halo atom, e.g. chloro or bromo and the like, with an intermediate of formula (XIX) in the presence of sodium hydride, and a suitable solvent, such as for example tetrahydrofuran.



The compounds of formula (I) or (I') inhibit Glycogen synthase kinase 3 (GSK3), in particular glycogen synthase kinase 3 beta (GSK3 β). They are selective Glycogen synthase kinase 3 inhibitors. Specific inhibitory compounds are superior therapeutic agents since they are characterized by a greater efficacy and lower toxicity by virtue of their specificity.

Synonyms for GSK3 are tau protein kinase I (TPK I), FA (Factor A) kinase, kinase FA and ATP-citrate lysase kinase (ACLK).

Glycogen synthase kinase 3 (GSK3), which exists in two isoforms, i.e. GSK3 α and GSK3 β , is a proline-directed serine/threonine kinase originally identified as an enzyme that phosphorylates glycogen synthase. However, it has been demonstrated that GSK3 phosphorylates numerous proteins in vitro such as glycogen synthase, phosphatase inhibitor I-2, the type-II subunit of cAMP-dependent protein kinase, the G-subunit of phosphatase-1, ATP-citrate lyase, acetyl coenzyme A carboxylase, myelin basic protein, a microtubule-associated protein, a neurofilament protein, an N-CAM cell adhesion molecule, nerve growth factor receptor, c-Jun transcription factor, JunD transcription factor, c-Myb transcription factor, c-Myc transcription factor, L-Myc transcription factor, adenomatous polyposis coli tumor suppressor protein, tau protein and β -catenin.

The above-indicated diversity of proteins which may be phosphorylated by GSK3 implies that GSK3 is implicated in numerous metabolic and regulatory processes in cells.

GSK3 inhibitors may therefore be useful in the prevention or treatment of diseases mediated through GSK3 activity such as bipolar disorder (in particular manic depression), diabetes, Alzheimer's disease, leukopenia, FTDP-17 (Fronto-temporal dementia associated with Parkinson's disease), cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy, Pick's disease, Niemann Pick's disease type C, Dementia Pugilistica, dementia with tangles only, dementia with tangles and calcification, Down syndrome, myotonic dystrophy, Parkinsonism-dementia complex of Guam, aids related dementia, Postencephalic Parkinsonism, prion diseases with tangles, subacute sclerosing panencephalitis, frontal lobe degeneration (FLD), argyrophilic grains disease, subacute sclerotizing panencephalitis (SSPE) (late complication of viral infections in the central nervous system), inflammatory diseases, cancer, dermatological disorders such as baldness, neuronal damage, schizophrenia, pain, in particular neuropathic pain. GSK3 inhibitors can also be used to inhibit sperm motility and can therefore be used as male contraceptives.

In particular, the compounds of the present invention are useful in the prevention or treatment of Alzheimer's disease, diabetes, especially type 2 diabetes (non insulin dependent diabetes).

The major neuropathological landmarks in Alzheimer's disease are neuronal loss, the deposition of amyloid fibers and paired helical filaments (PHF) or neurofibrillary tangles (NFT). Tangle formation appears to be the consequence of accumulation of aberrantly phosphorylated tau protein. This aberrant phosphorylation destabilizes neuronal cytoskeleton, which leads to reduced axonal transport, deficient functioning and ultimately neuronal death. The density of neurofibrillary tangles has been shown to parallel duration and severity of Alzheimer's disease. Reduction of the degree of tau phosphorylation can provide for neuroprotection and can prevent or treat Alzheimer's disease or can slow the progression of the disease. As mentioned hereinabove, GSK3 phosphorylates tau protein. Thus compounds having an inhibitory activity for GSK3 may be useful for the prevention or the treatment of Alzheimer's disease.

Insulin regulates the synthesis of the storage polysaccharide glycogen. The rate-limiting step in the glycogen synthesis is catalyzed by the enzyme glycogen synthase. It is believed that glycogen synthase is inhibited by phosphorylation and that insulin stimulates glycogen synthase by causing a net decrease in the phosphorylation of this

enzym. Thus, in order to activate glycogen synthase, insulin must either activate phosphatases or inhibit kinases, or both.

It is believed that glycogen synthase is a substrate for glycogen synthase kinase 3 and that insulin inactivates GSK3 thereby promoting the dephosphorylation of glycogen synthase.

In addition to the role of GSK3 in insulin-induced glycogen synthesis, GSK3 may also play a role in insulin resistance. It is believed that GSK3 dependent Insulin Receptor Substrate-1 phosphorylation contributes to insulin resistance.

Therefore, GSK3 inhibition may result in the increased deposition of glycogen and a concomitant reduction of blood glucose, thus mimicing the hypoglycemic effect of insulin. GSK3 inhibition provides an alternative therapy to manage insulin resistance commonly observed in non insulin dependent diabetes mellitus and obesity. GSK3 inhibitors may thus provide a novel modality for the treatment of type 1 and type 2 diabetes.

GSK3 inhibitors, in particular GSK3 β inhibitors, may also be indicated for use in the prevention or the treatment of pain, in particular neuropathic pain.

After axotomy or chronic constriction injury, neuronal cells die through an apoptotic pathway and the morphological changes correlate with the onset of hyperalgesia and/or allodynia.

The induction of apoptosis is probably triggered by a reduced supply of neurotrophic factors as the time course of neuronal loss is positively altered by administration of neurotrophins. GSK, in particular GSK3 β , has been shown to be involved in the initiation of the apoptotic cascade and trophic factor withdrawal stimulates the GSK3 β apoptosis pathway.

In view of the above, GSK3 β inhibitors might reduce signals of and even prevent levels of neuropathic pain.

Due to their GSK3 inhibitory properties, particularly their GSK3 β inhibitory properties, the compounds of formula (I) or (I'), their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms thereof, are useful to prevent or treat GSK3 mediated diseases, in particular GSK3 β mediated diseases, such as bipolar disorder (in particular manic depression), diabetes, Alzheimer's disease, leukopenia, FTDP-17 (Fronto-temporal dementia associated with Parkinson's disease), cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy, Pick's disease, Niemann Pick's disease type C, Dementia Pugilistica, dementia with tangles only, dementia with tangles and calcification, Down

syndrome, myotonic dystrophy, Parkinsonism-dementia complex of Guam, aids related dementia, Postencephalic Parkinsonism, prion diseases with tangles, subacute sclerosing panencephalitis, frontal lobe degeneration (FLD), argyrophilic grains disease, subacute sclerotizing panencephalitis (SSPE) (late complication of viral infections in the central nervous system), inflammatory diseases, cancer, dermatological disorders such as baldness, neuronal damage, schizophrenia, pain, in particular neuropathic pain. The present compounds are also useful as male contraceptives. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals suffering from disease mediated through GSK3, in particular GSK3 β , or they may be useful to prevent warm-blooded animals to suffer from disease mediated through GSK3, in particular GSK3 β . More in particular, the compounds of the present invention may be useful in the treatment of warm-blooded animals suffering from Alzheimer's disease, diabetes, especially type 2 diabetes, cancer, inflammatory diseases or bipolar disorder.

In view of the above described pharmacological properties, the compounds of formula (I) or any subgroup thereof, their N-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms, may be used as a medicine. In particular, the present compounds can be used for the manufacture of a medicament for treating or preventing diseases mediated through GSK3, in particular GSK3 β . More in particular, the present compounds can be used for the manufacture of a medicament for treating or preventing Alzheimer's disease, diabetes, especially type 2 diabetes, cancer, inflammatory diseases or bipolar disorder.

In view of the utility of the compounds of formula (I) or (I'), there is provided a method of treating warm-blooded animals, including humans, suffering from or a method of preventing warm-blooded animals, including humans, to suffer from diseases mediated through GSK3, in particular GSK3 β , more in particular a method of treating or preventing Alzheimer's disease, diabetes, especially type 2 diabetes, cancer, inflammatory diseases or bipolar disorder. Said method comprises the administration, preferably oral administration, of an effective amount of a compound of formula (I) or (I'), a N-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

The present invention also provides compositions for preventing or treating diseases mediated through GSK3, in particular GSK3 β , comprising a therapeutically effective amount of a compound of formula (I) or (I') and a pharmaceutically acceptable carrier

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or diluent.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate
5 compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of
10 preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of
15 oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are
20 obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case
25 appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in
30 minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. The compounds of the present invention may also be administered via inhalation or
35 insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry

powder. Any system developed for the delivery of solutions, suspensions or dry powders via oral or nasal inhalation or insufflation are suitable for the administration of the present compounds.

- 5 It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required
- 10 pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

- The present compounds are orally active compounds, and are preferably orally
- 15 administered.

- The exact dosage, the therapeutically effective amount and frequency of administration depends on the particular compound of formula (I) or (I') used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other
- 20 medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

- 25 When used as a medicament to prevent or treat Alzheimer's disease, the compounds of formula (I) or (I') may be used in combination with other conventional drugs used to combat Alzheimer's disease, such as galantamine, donepezil, rivastigmine or tacrine. Thus, the present invention also relates to the combination of a compound of formula (I) or (I') and another agent capable of preventing or treating Alzheimer's disease. Said
- 30 combination may be used as a medicine. The present invention also relates to a product containing (a) a compound of formula (I) or (I'), and (b) another agent capable of preventing or treating Alzheimer's disease, as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of Alzheimer's disease. The different drugs may be combined in a single preparation together with
- 35 pharmaceutically acceptable carriers.

When used as a medicament to prevent or treat type 2 diabetes, the compounds of formula (I) or (I') may be used in combination with other conventional drugs used to combat type 2 diabetes, such as glibenclamide, chlorpropamide, gliclazide, glipizide, gliquidon, tolbutamide, metformin, acarbose, miglitol, nateglinide, repaglinide, 5 acetohexamide, glimepiride, glyburide, tolazamide, troglitazone, rosiglitazone, pioglitazone, isaglitazone.

Thus, the present invention also relates to the combination of a compound of formula (I) or (I') and another agent capable of preventing or treating type 2 diabetes. Said combination may be used as a medicine. The present invention also relates to a product 10 containing (a) a compound of formula (I) or (I'), and (b) another agent capable of preventing or treating type 2 diabetes, as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of type 2 diabetes. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers.

15

When used as a medicament to prevent or treat cancer, the compounds of formula (I) or (I') may be used in combination with other conventional drugs used to combat cancer such as platinum coordination compounds for example cisplatin or carboplatin; taxane compounds for example paclitaxel or docetaxel; camptothecin compounds for example 20 irinotecan or topotecan; anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine; anti-tumour nucleoside derivatives for example 5-fluorouracil, gemcitabine or capecitabine; nitrogen mustard or nitrosourea alkylating agents for example cyclophosphamide, chlorambucil, carmustine or lomustine; anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin or idarubicin; HER2 25 antibodies for example trastuzumab; and anti-tumour podophyllotoxin derivatives for example etoposide or teniposide; and antiestrogen agents including estrogen receptor antagonists or selective estrogen receptor modulators preferably tamoxifen, or alternatively toremifene, droloxifene, faslodex and raloxifene; aromatase inhibitors such as exemestane, anastrozole, letrozole and vorozole; differentiating agents for 30 example retinoids, vitamin D and DNA methyl transferase inhibitors for example azacytidine; kinase inhibitors for example flavoperidol and imatinib mesylate or farnesyltransferase inhibitors for example R115777.

Thus, the present invention also relates to the combination of a compound of formula (I) or (I') and another agent capable of preventing or treating cancer. Said combination 35 may be used as a medicine. The present invention also relates to a product containing (a) a compound of formula (I) or (I'), and (b) another agent capable of preventing or treating cancer, as a combined preparation for simultaneous, separate or sequential use

in the prevention or treatment of cancer. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers.

When used as a medicament to prevent or treat bipolar disorder, the compounds of formula (I) or (I') may be used in combination with other conventional drugs used to combat bipolar disorder such as atypical antipsychotics, anti-epileptics, benzodiazepines, lithium salts, for example olanzapine, risperidone, carbamazepine, valproate, topiramate.

Thus, the present invention also relates to the combination of a compound of formula (I) or (I') and another agent capable of preventing or treating bipolar disorder. Said combination may be used as a medicine. The present invention also relates to a product containing (a) a compound of formula (I) or (I'), and (b) another agent capable of preventing or treating bipolar disorder, as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of bipolar disorder. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers.

When used as a medicament to prevent or treat inflammatory diseases, the compounds of formula (I) or (I') may be used in combination with other conventional drugs used to combat inflammatory diseases such as steroids, cyclooxygenase-2 inhibitors, non-steroidal-anti-inflammatory drugs, TNF- α antibodies, such as for example acetyl salicylic acid, bufexamac, diclofenac potassium, sulindac, diclofenac sodium, ketorolac trometamol, tolmetine, ibuprofen, naproxen, naproxen sodium, tiaprofen acid, flurbiprofen, mefenamic acid, niflumonic acid, meclofenamate, indomethacin, proglumetacine, ketoprofen, nabumetone, paracetamol, piroxicam, tenoxicam, nimesulide, fenylbutazon, tramadol, beclomethasone dipropionate, betamethasone, beclomethasone, budesonide, fluticasone, mometasone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, celecoxib, rofecoxib, infliximab, leflunomide, etanercept, CPH 82, methotrexate, sulfasalazine.

Thus, the present invention also relates to the combination of a compound of formula (I) or (I') and another agent capable of preventing or treating inflammatory diseases. Said combination may be used as a medicine. The present invention also relates to a product containing (a) a compound of formula (I) or (I'), and (b) another agent capable of preventing or treating inflammatory diseases, as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of inflammatory

disorders. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers.

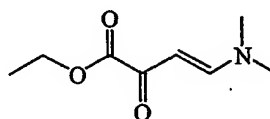
Experimental part

- 5 Hereinafter, "DIPE" is defined as diisopropyl ether, "DMA" is defined as *N,N*-dimethylacetamide.

A. Preparation of the intermediate compounds

Example A1

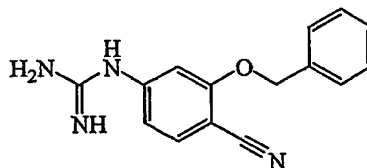
The preparation of intermediate 1



- 10 1,1-Diethoxy-*N,N*-dimethylmethanamine (0.153 mol) was added over 15 minutes to ethyl 2-oxopropanoate (0.153 mol) at room temperature while vigorously stirring. The temperature was kept below 30°C. The reaction mixture was heated to 80°C for 24 hours. The residue was purified by distillation, yielding 9.8g (37.4%) of intermediate 1.

Example A2

The preparation of intermediate 2

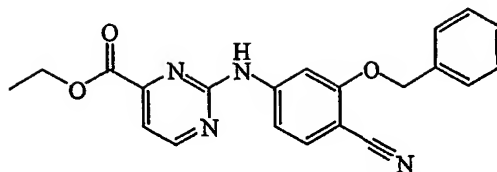


- 15 A mixture of 4-amino-2-(2-phenylethoxy)benzonitrile (0.012 mol) in 1,1'-oxybis[2-methoxyethane] (50 ml) was stirred at 100°C, cyanamide (1 ml) was added dropwise. The reaction mixture was stirred at 100°C for 30 minutes and at room temperature overnight. Extra cyanamide (1 ml) was added and the reaction mixture was stirred at 100°C for 24 hours. Extra cyanamide (1 ml) was added and the reaction mixture was stirred further at 100°C for 24 hours. The solvent was evaporated. The residue (6.3g) was purified by high-performance liquid chromatography over
20 Hyperprep C18 HS BDS (eluent : (0.5% NH₄Ac in H₂O/CH₃CN 90/10)/MeOH/CH₃CN 75/25/0; 0/50/50; 0/0/100). The first fraction was collected and the solvent was evaporated, yielding 1.36g (42.6%) of intermediate 2.

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Example A3

The preparation of intermediate 3

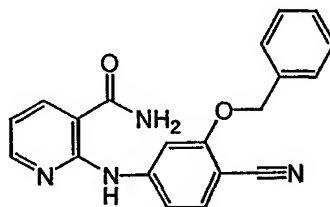


To a solution of intermediate 2 (0.00477 mol) in DMA (30 ml), intermediate 1 (0.0057 mol) was added. The reaction mixture was stirred for 1 hour at room temperature and overnight at 100°C. This mixture was again stirred at 100°C for 24 hours and then cooled to room temperature. The residue was poured out in a saturated NaCl-solution (300 ml), filtered and washed with H₂O. The precipitate was dissolved in 2-propanone and this solution was concentrated in vacuum. The obtained solid was crystallized from EtOH, filtered and dried at 40°C under vacuum, yielding 0.64g (35.8%) of intermediate 3.

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B. Preparation of the final compoundsExample B1

Preparation of compound 1

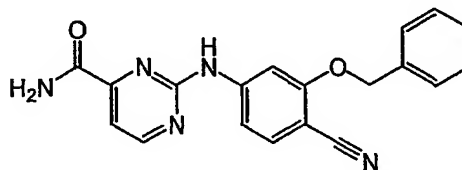


A mixture of 4-amino-2-(phenylmethoxy)-benzonitrile (0.0026 mol) and 2-chloro-3-pyridinecarboxamide (0.0026 mol) was stirred at 150°C for 10 minutes, taken up in CH₂Cl₂/CH₃OH and washed with H₂O. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 98/2/0.1; 15-35µm). The pure fractions were collected and the solvent was evaporated. The residue (0.21 g) was crystallized from CH₃OH/diethyl ether. The precipitate was filtered off and dried, yielding 0.2g of compound 1 (22%) (mp.: 232°C).

20

Example B2

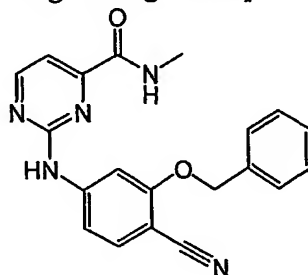
a) Preparation of compound 2



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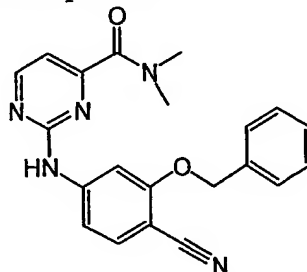
A mixture of intermediate 3 (0.0027 mol) in $\text{NH}_3/\text{CH}_3\text{OH}$ (30 ml) was stirred for 1 day at room temperature. The resulting precipitate was filtered off, washed with methanol and DIPE, then dried (vacuum, 50 °C), yielding 0.600 g of compound 2 (65%).

b) Preparation of compound 3



Intermediate 3 (0.0027 mol) in CH_3NH_2 in EtOH (15 ml) was stirred at room temperature for 1 day. The precipitate was filtered off, washed with MeOH and DIPE and dried (50°C, vacuum), yielding 0.7g of compound 3.

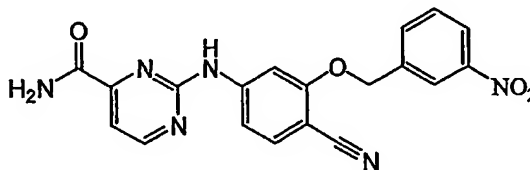
c) Preparation of compound 4

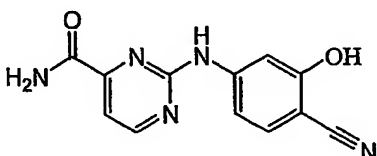


A mixture of intermediate 3 (0.0027 mol) and $(\text{CH}_3)_2\text{NH}$ (1.2 g) in EtOH (40 ml) was stirred at room temperature for 3 days. The solvent was evaporated and the residue was purified by flash column chromatography over silica gel (eluent : $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99.5/0.5; 99/1). The product fractions were collected and the solvent was evaporated. The residue was stirred in DIPE and the formed precipitate was filtered off, washed and dried (50°C, vacuum), yielding 0.21g of compound 4.

Example B3

a) Preparation of compound 5



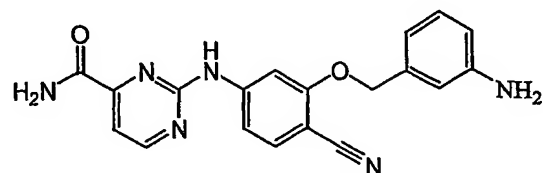
A mixture of  (compound 6; prepared according to

Example B2a)) (0.016 mol), 1-(chloromethyl)-3-nitro-benzene (0.016 mol), K_2CO_3 (0.016 mol) and KI (catalytic quantity) in DMA (70ml) was stirred at 60°C for 1 day.

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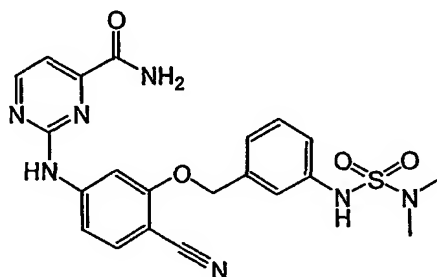
The reaction mixture was concentrated under reduced pressure. The residue was stirred in H₂O. The precipitate was filtered off, washed and dried (vacuum; 60°C), yielding 5.7g of compound 5.

b) Preparation of compound 7



Compound 5 (0.009 mol) in DMA (250 ml) was hydrogenated at room temperature with Pd/C 5% (1g) as a catalyst in the presence of thiophene solution (1 ml). After uptake of H₂ (3 equiv), the catalyst was filtered off and the solvent was evaporated, yielding 2.9g of compound 7.

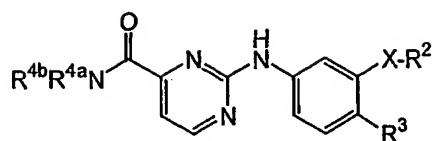
c) Preparation of compound 8



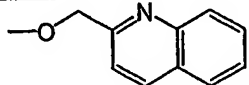
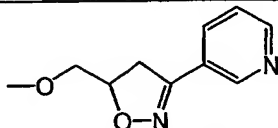
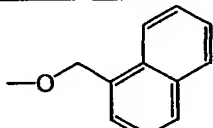
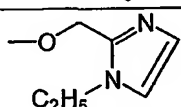
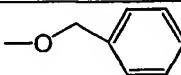
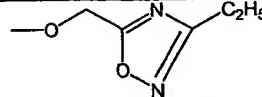
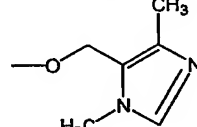
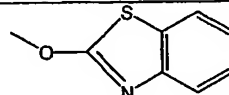
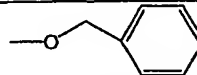
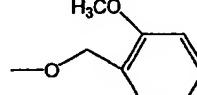
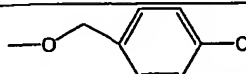
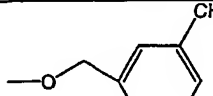
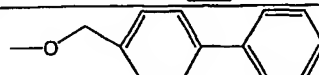
A mixture of compound 7 (0.0028 mol) and Et₃N (0.0031 mol) in DMA (25 ml) was stirred at room temperature. *N,N*-dimethylsulfamoyl chloride (0.0031 mol) was added dropwise at room temperature and the mixture was stirred for 1 day. More Et₃N (0.0031 mol) and *N,N*-dimethylsulfamoyl chloride (0.0031mol) were added and the mixture was stirred for another day at room temperature. The solvent was evaporated. The residue was purified by high performance liquid chromatography over hyperprep C18 BDS (eluent : (0.5% NH₄OAc in H₂O/CH₃CN 90/10)/MeOH/CH₃CN 75/25/0; 0/50/50; 0/0/100). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried (vacuum; 50°C), yielding 0.08 g of compound 8.

Tables 1 and 2 list the compounds of formula (I) which were prepared according to one of the above examples.

Table 1



Comp. no	Exp. no.	X-R ²	R ³	R ^{4a}	R ^{4b}
2	B2a	-O-CH ₂ C ₆ H ₅	-CN	H	H
3	B2b	-O-CH ₂ C ₆ H ₅	-CN	CH ₃	H
9	B3a		-CN	H	H
10	B3a		-CN	H	H
11	B3a		-CN	H	H
12	B3a	-O-CH ₂ CH ₂ N(CH ₃) ₂	-CN	H	H
13	B3a		-CN	H	H
14	B3a		-CN	H	H
15	B3a		-CN	H	H
16	B3a		-CN	H	H
17	B3a		-CN	H	H
18	B3a		-CN	H	H
19	B3a		-CN	H	H
20	B3a		-CN	H	H

Comp. no	Exp. no.	X-R ²	R ³	R ^{4a}	R ^{4b}
21	B3a		-CN	H	H
22	B3a		-CN	H	H
23	B3a		-CN	H	H
24	B3a		-CN	H	H
25	B2a		H	H	H
26	B3a		-CN	H	H
27	B3a		-CN	H	H
28	B3a		-CN	H	H
29	B2a	-H	-CN	H	H
4	B2c		-CN	CH ₃	CH ₃
30	B3a		-CN	H	H
31	B3a		-CN	H	H
32	B3a		-CN	H	H
33	B3a		-CN	H	H

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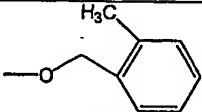
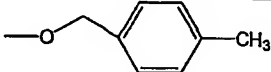
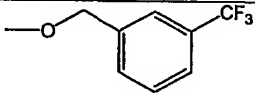
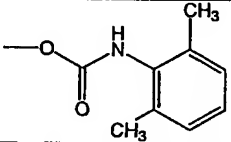
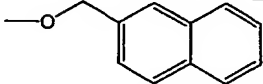
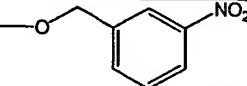
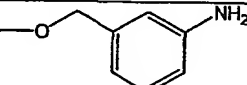
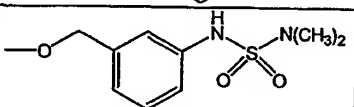
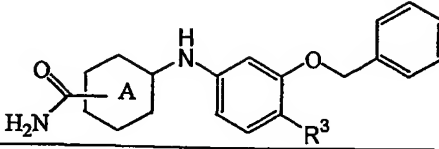
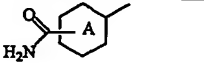
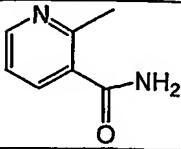
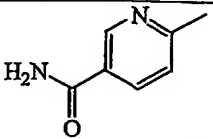
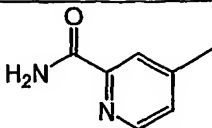
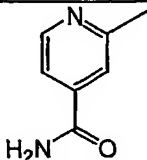
Comp. no	Exp. no.	X-R ²	R ³	R ^{4a}	R ^{4b}
34	B3a		-CN	H	H
35	B3a		-CN	H	H
36	B3a		-CN	H	H
37	B3a		-CN	H	H
38	B3a		-CN	H	H
6	B2a	-OH	-CN	H	H
5	B3a		-CN	H	H
7	B3b		-CN	H	H
8	B3c		-CN	H	H

Table 2



Comp. no	Exp. no.		R ³	Physical data
1	B1		-CN	
39	B2a		-CN	

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40	B1		-CN	
41	B2a		-CN	mp.:217°C

C. Pharmacological Example

The pharmacological activity of the present compounds was examined using the following test.

- 5 GSK3beta assays were performed at 25°C in a 100 µl reaction volume of 25mM Tris (pH 7.4) containing 10 mM MgCl₂, 1 mM DTT, 0.1 mg/ml BSA, 5% glycerol and containing 19 nM GSK3β, 5 µM biotinylated phosphorylated CREB peptide, 1 µM ATP, 2nM ATP-P³³ and a suitable amount of a test compound of formula (I) or (I').
- 10 After one hour, the reaction was terminated by adding 70 µl of Stop mix (1 mM ATP, 18 mg/ml streptavidin coated PVT SPA bead pH 11.0). The beads to which the phosphorylated CREB peptide is attached were allowed to settle for 30 minutes and the radioactivity of the beads was counted in a microtiterplate scintillation counter and compared with the results obtained in a control experiment (without the presence of a
- 15 test compound) in order to determine the percentage of GSK3β inhibition. The IC₅₀ value, i.e. the concentration (M) of the test compound at which 50 % of GSK3β is inhibited, was calculated from the dose response curve obtained by performing the above-described GSK3β assay in the presence of different amounts of the test compound.
- 20 Table 3 lists pIC₅₀ values (-log IC₅₀ (M)) obtained in the above-described test for the present compounds.

Table 3

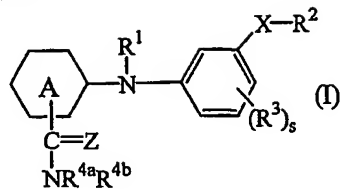
Comp. No.	pIC ₅₀
12	6.05
19	6.34
26	6.36
36	6.39
9	6.42

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Comp. No.	pIC ₅₀
11	6.58
17	6.61
22	6.63
34	6.75
28	6.79
35	6.81
29	6.83
14	6.86
15	6.88
10	6.96
31	7.02
25	7.04
23	7.09
32	7.19
18	7.24
3	7.26
38	7.26
13	7.28
2	7.30
24	7.32
30	7.33
16	7.41
21	7.60
8	7.68

Claims

1. A compound of formula



a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein

Z represents O or S;

ring A is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl;

R¹ is hydrogen; aryl; formyl; C₁₋₆alkylcarbonyl; C₁₋₆alkyl; C₁₋₆alkyloxycarbonyl;

C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylcarbonyloxy; C₁₋₆alkyloxyC₁₋₆alkylcarbonyl optionally substituted with C₁₋₆alkyloxycarbonyl;

X is -NR¹-; -NH-NH-; -N=N-; -O-; -C(=O)-; -C(=S)-; -O-C(=O)-; -C(=O)-O-;

-O-C(=O)-C₁₋₆alkyl-; -C(=O)-O-C₁₋₆alkyl-; -O-C₁₋₆alkyl-C(=O)-;

-C(=O)-C₁₋₆alkyl-O-; -O-C(=O)-NR¹-; -NR¹-C(=O)-O-; -O-C(=O)-C(=O)-;

-C(=O)-NR¹-; -NR¹-C(=O)-; -C(=S)-NR¹-; -NR¹-C(=S)-; -NR¹-C(=O)-NR¹-;

-NR¹-C(=S)-NR¹-; -NR¹-S(=O)-NR¹-; -NR¹-S(=O)₂-NR¹-; -C₁₋₆alkyl-C(=O)-NR¹-;

-O-C₁₋₆alkyl-C(=O)-NR¹-; -C₁₋₆alkyl-O-C(=O)-NR¹-; -C₁₋₆alkyl-; -O-C₁₋₆alkyl-;

-C₁₋₆alkyl-O-; -NR¹-C₁₋₆alkyl-; -C₁₋₆alkyl-NR¹-; -NR¹-C₁₋₆alkyl-NR¹-;

-NR¹-C₁₋₆alkyl-C₃₋₇cycloalkyl-; -C₂₋₆alkenyl-; -C₂₋₆alkynyl-; -O-C₂₋₆alkenyl-;

-C₂₋₆alkenyl-O-; -NR¹-C₂₋₆alkenyl-; -C₂₋₆alkenyl-NR¹-; -NR¹-C₂₋₆alkenyl-NR¹-;

-NR¹-C₂₋₆alkenyl-C₃₋₇cycloalkyl-; -O-C₂₋₆alkynyl-; -C₂₋₆alkynyl-O-;

-NR¹-C₂₋₆alkynyl-; -C₂₋₆alkynyl-NR¹-; -NR¹-C₂₋₆alkynyl-NR¹-;

-NR¹-C₂₋₆alkynyl-C₃₋₇cycloalkyl-; -O-C₁₋₆alkyl-O-; -O-C₂₋₆alkenyl-O-;

-O-C₂₋₆alkynyl-O-; -CHOH-; -S-; -S(=O)-; -S(=O)₂-; -S(=O)-NR¹-; -S(=O)₂-NR¹-;

-NR¹-S(=O)-; -NR¹-S(=O)₂-; -S-C₁₋₆alkyl-; -C₁₋₆alkyl-S-; -S-C₂₋₆alkenyl-;

-C₂₋₆alkenyl-S-; -S-C₂₋₆alkynyl-; -C₂₋₆alkynyl-S-; -O-C₁₋₆alkyl-S(=O)₂- or a direct

bond;

R² is hydrogen, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, R²⁰, each of said groups

representing R² may optionally be substituted where possible with one or more

substituents each independently being selected from =S; =O; R¹⁵; hydroxy; halo;

nitro; cyano; R¹⁵-O-; SH; R¹⁵-S-; formyl; carboxyl; R¹⁵-C(=O)-; R¹⁵-O-C(=O)-;

R¹⁵-C(=O)-O-; R¹⁵-O-C(=O)-O-; -SO₃H; R¹⁵-S(=O)-; R¹⁵-S(=O)₂-; R⁵R⁶N;

R⁵R⁶N-C₁₋₆alkyl; R⁵R⁶N-C₃₋₇cycloalkyl; R⁵R⁶N-C₁₋₆alkyloxy; R⁵R⁶N-C(=O)-;

- $R^5R^6N-C(=S)-$; $R^5R^6N-C(=O)-NH-$; $R^5R^6N-C(=S)-NH-$; $R^5R^6N-S(=O)_n-$;
 $R^5R^6N-S(=O)_n-NH-$; $R^{15}-C(=S)-$; $R^{15}-C(=O)-NH-$; $R^{15}-O-C(=O)-NH-$;
 $R^{15}-S(=O)_n-NH-$; $R^{15}-O-S(=O)_n-NH-$; $R^{15}-C(=S)-NH-$; $R^{15}-O-C(=S)-NH-$;
 $R^{17}R^{18}N-Y_{1a}-$; $R^{17}R^{18}N-Y_2-NR^{16}-Y_{1-}$; $R^{15}-Y_2-NR^{19}-Y_{1-}$; $H-Y_2-NR^{19}-Y_{1-}$;
5 R^3 is hydrogen; hydroxy; halo; C_{1-6} alkyl; C_{1-6} alkyl substituted with cyano, hydroxy or
 $-C(=O)R^7$; C_{2-6} alkenyl; C_{2-6} alkenyl substituted with one or more halogen atoms or
cyano; C_{2-6} alkynyl; C_{2-6} alkynyl substituted with one or more halogen atoms or
cyano; C_{1-6} alkyloxy; C_{1-6} alkylthio; C_{1-6} alkyloxycarbonyl; C_{1-6} alkylcarbonyloxy;
carboxyl; cyano; nitro; amino; mono- or di(C_{1-6} alkyl)amino; polyhalo C_{1-6} alkyl;
10 polyhalo C_{1-6} alkyloxy; polyhalo C_{1-6} alkylthio; R^{21} ; $R^{21}-C_{1-6}$ alkyl; $R^{21}-O-$; $R^{21}-S-$;
 $R^{21}-C(=O)-$; $R^{21}-S(=O)_p-$; $R^7-S(=O)_p-$; $R^7-S(=O)_p-NH-$; $R^{21}-S(=O)_p-NH-$;
 $R^7-C(=O)-$; $-NHC(=O)H$; $-C(=O)NHNH_2$; $R^7-C(=O)-NH-$; $R^{21}-C(=O)-NH-$;
 $-C(=NH)R^7$; $-C(=NH)R^{21}$;
 R^{4a} or R^{4b} each independently are hydrogen, R^8 , $-Y_1-NR^9-Y_2-NR^{10}R^{11}$, $-Y_1-NR^9-Y_1-R^8$,
15 $-Y_1-NR^9R^{10}$;
 R^5 and R^6 each independently are hydrogen, R^8 , $-Y_1-NR^9-Y_2-NR^{10}R^{11}$, $-Y_1-NR^9-Y_1-R^8$,
 $-Y_1-NR^9R^{10}$, or
 R^5 and R^6 may together with the nitrogen to which they are attached form a saturated or
partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8
20 membered monocyclic heterocycle, each of said heterocycles may optionally be
substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} , or each of
said heterocycles may optionally be fused with a benzene ring, said benzene ring
being optionally substituted with one or more substituents selected from R^{12} , R^{13} and
 R^{14} ;
25 R^7 is C_{1-6} alkyl, C_{1-6} alkyloxy, amino, mono- or di(C_{1-6} alkyl)amino or polyhalo C_{1-6} alkyl;
 R^8 is C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; a monocyclic, bicyclic or tricyclic saturated
carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a
monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or
tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated
30 heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; C_{1-6} alkyl
substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a
monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic,
bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic
saturated heterocycle or with a monocyclic, bicyclic or tricyclic partially saturated
35 heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of
said groups representing R^8 may optionally be substituted with one or more
substituents selected from R^{12} , R^{13} and R^{14} ;

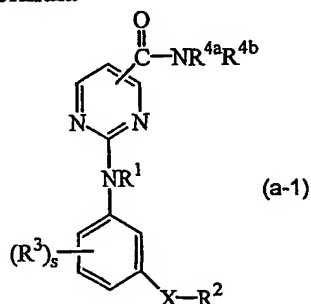
R^9 , R^{10} and R^{11} each independently are hydrogen or R^8 , or
 any two of R^9 , R^{10} and R^{11} may together be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby
 forming a saturated or partially saturated monocyclic 3 to 8 membered heterocycle
 or an aromatic 4 to 8 membered monocyclic heterocycle together with the nitrogen
 atoms to which they are attached, each of said heterocycles may optionally be
 5 substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;
 R^{12} , R^{13} and R^{14} each independently are hydrogen; R^{15} ; hydroxy; halo; nitro; cyano;
 R^{15} -O-; SH; R^{15} -S-; formyl; carboxyl; R^{15} -C(=O)-; R^{15} -O-C(=O)-; R^{15} -C(=O)-O-;
 R^{15} -O-C(=O)-O-; $-SO_3H$; R^{15} -S(=O)-; R^{15} -S(=O)₂-; $R^{15}R^{16}N$ -S(=O)-;
 10 $R^{15}R^{16}N$ -S(=O)₂-; $R^{17}R^{18}N$ -Y₁-; $R^{17}R^{18}N$ -Y₂-NR¹⁶-Y₁-; R^{15} -Y₂-NR¹⁹-Y₁-;
 H-Y₂-NR¹⁹-Y₁-; oxo, or
 any two of R^{12} , R^{13} and R^{14} may together be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby
 forming a saturated or partially saturated monocyclic 3 to 8 membered carbo – or
 heterocycle or an aromatic 4 to 8 membered monocyclic carbo – or heterocycle
 15 together with the atoms to which they are attached, or
 any two of R^{12} , R^{13} and R^{14} may together be $-O-(CH_2)_r-O-$ thereby forming a saturated,
 partially saturated or aromatic monocyclic 4 to 8 membered carbo – or heterocycle
 together with the atoms to which they are attached;
 R^{15} is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, a monocyclic, bicyclic or tricyclic saturated
 20 carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a
 monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or
 tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated
 heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; C_{1-6} alkyl
 substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a
 25 monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic,
 bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic
 saturated heterocycle or with a monocyclic, bicyclic or tricyclic partially saturated
 heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of
 said substituents representing R^{15} may optionally be substituted with one or more
 30 substituents selected from R^{12} , R^{13} and R^{14} ; or each of said carbocycles or
 heterocycles may optionally be fused with a benzene ring, said benzene ring being
 optionally substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;
 R^{16} , R^{17} , R^{18} and R^{19} each independently are hydrogen or R^{15} , or
 R^{17} and R^{18} , or R^{15} and R^{19} may together be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby
 35 forming a saturated or partially saturated monocyclic 3 to 8 membered heterocycle
 or an aromatic 4 to 8 membered monocyclic heterocycle, each of said heterocycles

- may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ; or
- R^{17} and R^{18} together with R^{16} may be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby forming a saturated or partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8 membered monocyclic heterocycle together with the nitrogen atoms to which they are attached, each of said heterocycles may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;
- R^{20} is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle;
- R^{21} is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle, each of said carbocycles or heterocycles representing R^{21} may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;
- Y_{1a} is $-Y_3-S(=O)-Y_4-$; $-Y_3-S(=O)_2-Y_4-$; $-Y_3-C(=O)-Y_4-$; $-Y_3-C(=S)-Y_4-$; $-Y_3-O-Y_4-$; $-Y_3-S-Y_4-$; $-Y_3-O-C(=O)-Y_4-$ or $-Y_3-C(=O)-O-Y_4-$;
- Y_1 or Y_2 each independently are a direct bond, $-Y_3-S(=O)-Y_4-$; $-Y_3-S(=O)_2-Y_4-$; $-Y_3-C(=O)-Y_4-$; $-Y_3-C(=S)-Y_4-$; $-Y_3-O-Y_4-$; $-Y_3-S-Y_4-$; $-Y_3-O-C(=O)-Y_4-$ or $-Y_3-C(=O)-O-Y_4-$;
- Y_3 or Y_4 each independently are a direct bond, C_{1-6} alkanediyl, C_{2-6} alkenediyl or C_{2-6} alkynediyl;
- n is 1 or 2;
- m is 1 or 2;
- p is 1 or 2;
- r is 1 to 5;
- s is 1 to 3;
- aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, cyano, nitro, polyhalo C_{1-6} alkyl and polyhalo C_{1-6} alkyloxy;
- provided that $-X-R^2$ and/or R^3 is other than hydrogen; and
- provided that the following compounds

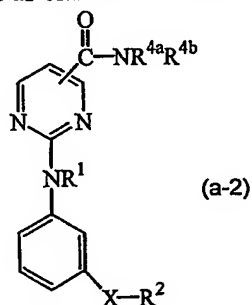
-54-

N-methoxy-*N*-methyl-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinecarboxamide and *N*-phenyl-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinecarboxamide are not included.

- 5 2. A compound as claimed in claim 1 wherein ring A is pyrimidinyl, pyrazinyl or pyridazinyl and wherein R₃ is other than C₁₋₆alkyloxy or polyhaloC₁₋₆alkyloxy.
3. A compound as claimed in claim 1 or 2 provided that -X- is other than a direct bond or -C₁₋₆alkyl-.
- 10 4. A compound as claimed in any one of claims 1 to 3 wherein the compound has the following formula

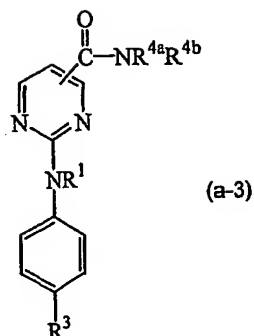


- 15 5. A compound as claimed in claim 1 wherein the compound has the following formula



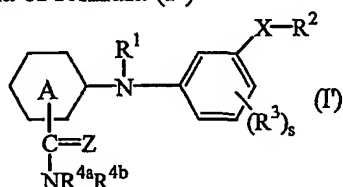
6. A compound as claimed in claim 1 or 2 wherein the compound has the following formula

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7. A compound as claimed in claim 1 wherein the compound is
- 2-[[[4-cyano-3-[[[(dimethylamino)sulfonyl]amino]phenyl]methoxy]phenyl]amino]-4-pyrimidinecarboxamide;
- 5 2-[[[4-cyano-3-[(2-quinolinylmethoxy)phenyl]amino]-4-pyrimidinecarboxamide;
- 2-[[[4-cyano-3-[2-(4-fluorophenoxy)propoxy]phenyl]amino]-4-pyrimidinecarboxamide;
- 2-[[[4-cyano-3-[(2-methoxyphenyl)methoxy]phenyl]amino]-4-pyrimidinecarboxamide;
- 10 2-[[[4-cyano-3-[(1-ethyl-1*H*-imidazol-2-yl)methoxy]phenyl]amino]-4-pyrimidinecarboxamide;
- 2-[[[4-cyano-3-(phenylmethoxy)phenyl]amino]-4-pyrimidinecarboxamide;
- 2-[[[4-cyano-3-[(4-methoxyphenyl)methoxy]phenyl]amino]-4-pyrimidinecarboxamide;
- 15 2-[[[4-cyano-3-(2-naphthalenylmethoxy)phenyl]amino]-4-pyrimidinecarboxamide;
- a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.
- 20 8. A compound as claimed in claim 1 wherein the compound is
- 2-(3-benzyloxy-4-cyano-phenylamino)-nicotinamide;
- 6-(3-benzyloxy-4-cyano-phenylamino)-nicotinamide;
- 4-(3-benzyloxy-4-cyano-phenylamino)-pyridine-2-carboxylic acid amide;
- 2-(3-benzyloxy-4-cyano-phenylamino)-isonicotinamide;
- 25 a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.
9. A compound as claimed in any one of claims 1 to 8 for use as a medicine.

10. The use of a compound for the manufacture of a medicament for the prevention or the treatment of diseases mediated through GSK3, said compound being a compound of formula of formula (I')



- 5 a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein
Z represents O or S;
ring A is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl;
R¹ is hydrogen; aryl; formyl; C₁₋₆alkylcarbonyl; C₁₋₆alkyl; C₁₋₆alkyloxycarbonyl;
10 C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylcarbonyloxy; C₁₋₆alkyloxyC₁₋₆alkylcarbonyl optionally substituted with C₁₋₆alkyloxycarbonyl;
X is -NR¹-; -NH-NH-; -N=N-; -O-; -C(=O)-; -C(=S)-; -O-C(=O)-; -C(=O)-O-;
-O-C(=O)-C₁₋₆alkyl-; -C(=O)-O-C₁₋₆alkyl-; -O-C₁₋₆alkyl-C(=O)-;
15 -C(=O)-C₁₋₆alkyl-O-; -O-C(=O)-NR¹-; -NR¹-C(=O)-O-; -O-C(=O)-C(=O)-; -C(=O)-NR¹-; -NR¹-C(=O)-; -C(=S)-NR¹-; -NR¹-C(=S)-; -NR¹-C(=O)-NR¹-; -NR¹-C(=S)-NR¹-; -NR¹-S(=O)-NR¹-; -NR¹-S(=O)₂-NR¹-; -C₁₋₆alkyl-C(=O)-NR¹-; -O-C₁₋₆alkyl-C(=O)-NR¹-; -C₁₋₆alkyl-O-C(=O)-NR¹-; -C₁₋₆alkyl-; -O-C₁₋₆alkyl-; -C₁₋₆alkyl-O-;
-NR¹-C₁₋₆alkyl-; -C₁₋₆alkyl-NR¹-; -NR¹-C₁₋₆alkyl-NR¹-;
20 -NR¹-C₁₋₆alkyl-C₃₋₇cycloalkyl-; -C₂₋₆alkenyl-; -C₂₋₆alkynyl-; -O-C₂₋₆alkenyl-; -C₂₋₆alkenyl-O-; -NR¹-C₂₋₆alkenyl-; -C₂₋₆alkenyl-NR¹-; -NR¹-C₂₋₆alkenyl-NR¹-;
-NR¹-C₂₋₆alkenyl-C₃₋₇cycloalkyl-; -O-C₂₋₆alkynyl-; -C₂₋₆alkynyl-O-; -NR¹-C₂₋₆alkynyl-; -C₂₋₆alkynyl-NR¹-; -NR¹-C₂₋₆alkynyl-NR¹-;
-NR¹-C₂₋₆alkynyl-C₃₋₇cycloalkyl-; -O-C₁₋₆alkyl-O-; -O-C₂₋₆alkenyl-O-;
25 -O-C₂₋₆alkynyl-O-; -CHOH-; -S-; -S(=O)-; -S(=O)₂-; -S(=O)-NR¹-; -S(=O)₂-NR¹-; -NR¹-S(=O)-; -NR¹-S(=O)₂-; -S-C₁₋₆alkyl-; -C₁₋₆alkyl-S-; -S-C₂₋₆alkenyl-; -C₂₋₆alkenyl-S-; -S-C₂₋₆alkynyl-; -C₂₋₆alkynyl-S-; -O-C₁₋₆alkyl-S(=O)₂- or a direct bond;
R² is hydrogen, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, R²⁰, each of said groups
30 representing R² may optionally be substituted where possible with one or more substituents each independently being selected from =S; =O; R¹⁵; hydroxy; halo; nitro; cyano; R¹⁵-O-; SH; R¹⁵-S-; formyl; carboxyl; R¹⁵-C(=O)-; R¹⁵-O-C(=O)-; R¹⁵-C(=O)-O-; R¹⁵-O-C(=O)-O-; -SO₃H; R¹⁵-S(=O)-; R¹⁵-S(=O)₂-; R⁵R⁶N;

- $R^5R^6N-C_{1-6}alkyl$; $R^5R^6N-C_{3-7}cycloalkyl$; $R^5R^6N-C_{1-6}alkyloxy$; $R^5R^6N-C(=O)-$;
 $R^5R^6N-C(=S)-$; $R^5R^6N-C(=O)-NH-$; $R^5R^6N-C(=S)-NH-$; $R^5R^6N-S(=O)_n-$;
 $R^5R^6N-S(=O)_n-NH-$; $R^{15}-C(=S)-$; $R^{15}-C(=O)-NH-$; $R^{15}-O-C(=O)-NH-$;
 $R^{15}-S(=O)_n-NH-$; $R^{15}-O-S(=O)_n-NH-$; $R^{15}-C(=S)-NH-$; $R^{15}-O-C(=S)-NH-$;
 $R^{17}R^{18}N-Y_{1a}-$; $R^{17}R^{18}N-Y_2-NR^{16}-Y_1-$; $R^{15}-Y_2-NR^{19}-Y_1-$; $H-Y_2-NR^{19}-Y_1-$;
 R^3 is hydrogen; hydroxy; halo; $C_{1-6}alkyl$; $C_{1-6}alkyl$ substituted with cyano, hydroxy or
 $-C(=O)R^7$; $C_{2-6}alkenyl$; $C_{2-6}alkenyl$ substituted with one or more halogen atoms or
cyano; $C_{2-6}alkynyl$; $C_{2-6}alkynyl$ substituted with one or more halogen atoms or
cyano; $C_{1-6}alkyloxy$; $C_{1-6}alkylthio$; $C_{1-6}alkyloxycarbonyl$; $C_{1-6}alkylcarbonyloxy$;
carboxyl; cyano; nitro; amino; mono- or di($C_{1-6}alkyl$)amino; polyhalo $C_{1-6}alkyl$;
polyhalo $C_{1-6}alkyloxy$; polyhalo $C_{1-6}alkylthio$; R^{21} ; $R^{21}-C_{1-6}alkyl$; $R^{21}-O-$; $R^{21}-S-$;
 $R^{21}-C(=O)-$; $R^{21}-S(=O)_p-$; $R^7-S(=O)_p-$; $R^7-S(=O)_p-NH-$; $R^{21}-S(=O)_p-NH-$;
 $R^7-C(=O)-$; $-NHC(=O)H$; $-C(=O)NHNH_2$; $R^7-C(=O)-NH-$; $R^{21}-C(=O)-NH-$;
 $-C(=NH)R^7$; $-C(=NH)R^{21}$;
 R^{4a} or R^{4b} each independently are hydrogen, R^8 , $-Y_1-NR^9-Y_2-NR^{10}R^{11}$, $-Y_1-NR^9-Y_1-R^8$,
 $-Y_1-NR^9R^{10}$;
 R^5 and R^6 each independently are hydrogen, R^8 , $-Y_1-NR^9-Y_2-NR^{10}R^{11}$, $-Y_1-NR^9-Y_1-R^8$,
 $-Y_1-NR^9R^{10}$, or
 R^5 and R^6 may together with the nitrogen to which they are attached form a saturated or
partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8
membered monocyclic heterocycle, each of said heterocycles may optionally be
substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} , or each of
said heterocycles may optionally be fused with a benzene ring, said benzene ring
being optionally substituted with one or more substituents selected from R^{12} , R^{13} and
 R^{14} ;
 R^7 is $C_{1-6}alkyl$, $C_{1-6}alkyloxy$, amino, mono- or di($C_{1-6}alkyl$)amino or polyhalo $C_{1-6}alkyl$;
 R^8 is $C_{1-6}alkyl$; $C_{2-6}alkenyl$; $C_{2-6}alkynyl$; a monocyclic, bicyclic or tricyclic saturated
carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a
monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or
tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated
heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; $C_{1-6}alkyl$
substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a
monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic,
bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic
saturated heterocycle or with a monocyclic, bicyclic or tricyclic partially saturated
heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of

said groups representing R^8 may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;

R^9 , R^{10} and R^{11} each independently are hydrogen or R^8 , or
any two of R^9 , R^{10} and R^{11} may together be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby
5 forming a saturated or partially saturated monocyclic 3 to 8 membered heterocycle
or an aromatic 4 to 8 membered monocyclic heterocycle together with the nitrogen
atoms to which they are attached, each of said heterocycles may optionally be
substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;

R^{12} , R^{13} and R^{14} each independently are hydrogen; R^{15} ; hydroxy; halo; nitro; cyano;
10 R^{15} -O-; SH; R^{15} -S-; formyl; carboxyl; R^{15} -C(=O)-; R^{15} -O-C(=O)-; R^{15} -C(=O)-O-;
 R^{15} -O-C(=O)-O-; $-SO_3H$; R^{15} -S(=O)-; R^{15} -S(=O)₂-; $R^{15}R^{16}N$ -S(=O)-;
 $R^{15}R^{16}N$ -S(=O)₂-; $R^{17}R^{18}N$ -Y₁-; $R^{17}R^{18}N$ -Y₂-NR¹⁶-Y₁-; R^{15} -Y₂-NR¹⁹-Y₁-;
H-Y₂-NR¹⁹-Y₁-; oxo, or
any two of R^{12} , R^{13} and R^{14} may together be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby
15 forming a saturated or partially saturated monocyclic 3 to 8 membered carbo – or
heterocycle or an aromatic 4 to 8 membered monocyclic carbo – or heterocycle
together with the atoms to which they are attached, or
any two of R^{12} , R^{13} and R^{14} may together be $-O-(CH_2)_r-O-$ thereby forming a saturated,
partially saturated or aromatic monocyclic 4 to 8 membered carbo – or heterocycle
20 together with the atoms to which they are attached;

R^{15} is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, a monocyclic, bicyclic or tricyclic saturated
carbocycle; a monocyclic, bicyclic or tricyclic partially saturated carbocycle; a
monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or
tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated
25 heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle; C_{1-6} alkyl
substituted with a monocyclic, bicyclic or tricyclic saturated carbocycle or with a
monocyclic, bicyclic or tricyclic partially saturated carbocycle or with a monocyclic,
bicyclic or tricyclic aromatic carbocycle or with a monocyclic, bicyclic or tricyclic
saturated heterocycle or with a monocyclic, bicyclic or tricyclic partially saturated
30 heterocycle or with a monocyclic, bicyclic or tricyclic aromatic heterocycle; each of
said substituents representing R^{15} may optionally be substituted with one or more
substituents selected from R^{12} , R^{13} and R^{14} ; or each of said carbocycles or
heterocycles may optionally be fused with a benzene ring, said benzene ring being
optionally substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;

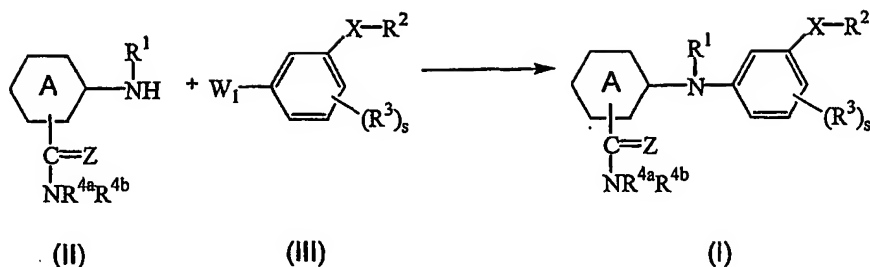
35 R^{16} , R^{17} , R^{18} and R^{19} each independently are hydrogen or R^{15} , or
 R^{17} and R^{18} , or R^{15} and R^{19} may together be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby
forming a saturated or partially saturated monocyclic 3 to 8 membered heterocycle

- or an aromatic 4 to 8 membered monocyclic heterocycle, each of said heterocycles may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ; or
- R^{17} and R^{18} together with R^{16} may be C_{1-6} alkanediyl or C_{2-6} alkenediyl thereby forming
- 5 a saturated or partially saturated monocyclic 3 to 8 membered heterocycle or an aromatic 4 to 8 membered monocyclic heterocycle together with the nitrogen atoms to which they are attached, each of said heterocycles may optionally be substituted with one or more substituents selected from R^{12} , R^{13} and R^{14} ;
- R^{20} is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic
- 10 or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle;
- R^{21} is a monocyclic, bicyclic or tricyclic saturated carbocycle; a monocyclic, bicyclic
- 15 or tricyclic partially saturated carbocycle; a monocyclic, bicyclic or tricyclic aromatic carbocycle; a monocyclic, bicyclic or tricyclic saturated heterocycle; a monocyclic, bicyclic or tricyclic partially saturated heterocycle; a monocyclic, bicyclic or tricyclic aromatic heterocycle, each of said carbocycles or heterocycles representing R^{21} may optionally be substituted with one or more substituents
- 20 selected from R^{12} , R^{13} and R^{14} ;
- Y_{1a} is $-Y_3-S(=O)-Y_4-$; $-Y_3-S(=O)_2-Y_4-$; $-Y_3-C(=O)-Y_4-$; $-Y_3-C(=S)-Y_4-$; $-Y_3-O-Y_4-$; $-Y_3-S-Y_4-$; $-Y_3-O-C(=O)-Y_4-$ or $-Y_3-C(=O)-O-Y_4-$;
- Y_1 or Y_2 each independently are a direct bond, $-Y_3-S(=O)-Y_4-$; $-Y_3-S(=O)_2-Y_4-$; $-Y_3-C(=O)-Y_4-$; $-Y_3-C(=S)-Y_4-$; $-Y_3-O-Y_4-$; $-Y_3-S-Y_4-$; $-Y_3-O-C(=O)-Y_4-$ or
- 25 $-Y_3-C(=O)-O-Y_4-$;
- Y_3 or Y_4 each independently are a direct bond, C_{1-6} alkanediyl, C_{2-6} alkenediyl or C_{2-6} alkynediyl;
- n is 1 or 2;
- m is 1 or 2;
- 30 p is 1 or 2;
- r is 1 to 5;
- s is 1 to 3;
- aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, cyano,
- 35 nitro, polyhalo C_{1-6} alkyl and polyhalo C_{1-6} alkyloxy;
- provided that $-X-R^2$ and/or R^3 is other than hydrogen.

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11. The use of a compound as defined in any one of claims 1 to 8 for the manufacture of a medicament for the prevention or the treatment of diseases mediated through GSK3.
- 5 12. The use of a compound as defined in claim 10 or 11 for the manufacture of a medicament for the prevention or the treatment of bipolar disorder (in particular manic depression), diabetes, Alzheimer's disease, leukopenia, FTDP-17 (Fronto-temporal dementia associated with Parkinson's disease), cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy, Pick's disease, Niemann Pick's disease
- 10 type C, Dementia Pugilistica, dementia with tangles only, dementia with tangles and calcification, Down syndrome, myotonic dystrophy, Parkinsonism-dementia complex of Guam, aids related dementia, Postencephalic Parkinsonism, prion diseases with tangles, subacute sclerosing panencephalitis, frontal lobe degeneration (FLD), argyrophilic grains disease, subacute sclerotizing panencephalitis (SSPE) (late
- 15 complication of viral infections in the central nervous system), inflammatory diseases, cancer, dermatological disorders, neuronal damage, schizophrenia, pain.
13. The use of a compound as claimed in claim 12 for the prevention or the treatment of Alzheimer's disease, diabetes, cancer, inflammatory diseases or bipolar disorder.
- 20 14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 8.
- 25 15. A process for preparing a pharmaceutical composition as claimed in claim 14 characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 8 is intimately mixed with a pharmaceutically acceptable carrier.
- 30 16. A process for preparing a compound as claimed in claim 1, characterized by a) reacting an intermediate of formula (II) with an intermediate of formula (III) in the presence of a suitable solvent and optionally in the presence of a suitable acid or a suitable base

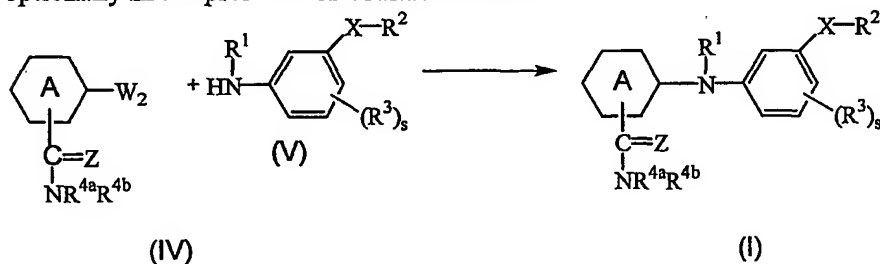
-61-



with W₁ representing a suitable leaving group and with R¹, R², R³, R^{4a}, R^{4b}, X, Z, s and ring A as defined in claim 1;

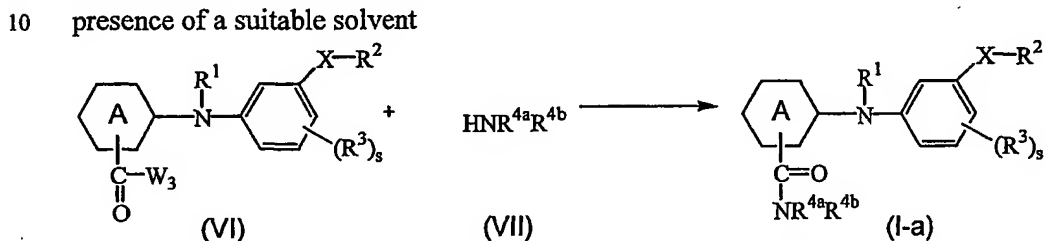
b) reacting an intermediate of formula (IV) with an intermediate of formula (V)

5 optionally in the presence of a suitable solvent



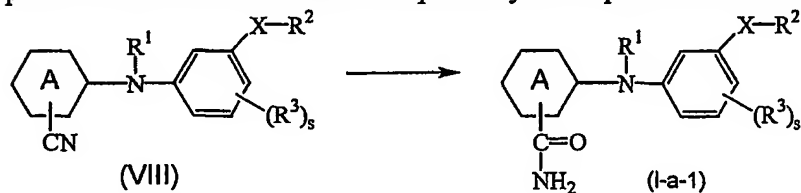
with W₂ representing a suitable leaving group and with R¹, R², R³, R^{4a}, R^{4b}, X, Z, s and ring A as defined in claim 1;

c) reacting an intermediate of formula (VI) with an intermediate of formula (VII) in the presence of a suitable solvent



with W₃ representing a suitable leaving group and with R¹, R², R³, R^{4a}, R^{4b}, X, s and ring A as defined in claim 1;

d) reacting an intermediate of formula (VIII) with a suitable oxidizing agent in the presence of a suitable solvent and optionally in the presence of a suitable base



with R¹, R², R³, X, s and ring A as defined in claim 1;

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- and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or
- 5 conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, quaternary amines or *N*-oxide forms thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/12067

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D213/82 C07D239/42 C07D413/12 C07D413/14 C07D407/12
C07D417/12 C07D401/12 C07D403/12 A61K31/505 A61P3/10
A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OSSELAERE ET AL: "anti-inflammatory 2-anilinonicotinamides" FARMACEUTISCH TIJDSCHRIFT VOOR BELGIE, ZOERSEL, BE, vol. 50, no. 4, 1973, pages 338-344, XP002129423 ISSN: 0771-2367 compound II p.338 and table p.342	1-3
X	US 5 264 437 A (WILHELM ROBERT S ET AL) 23 November 1993 (1993-11-23) column 9, intermediate 5	1-3
X	GB 1 401 549 A (HISAMITSU PHARMACEUTICAL CO) 16 July 1975 (1975-07-16) p.5 intermediate 12	1-3
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

15 January 2003

Date of mailing of the international search report

27/01/2003

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Schuemacher, A

INTERNATIONAL SEARCH REPORT

 Internat
 Application No
 PCT/EP 02/12067

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 198 551 A (LABORATOIRES UPSA, GENNEVILLIERS, FRANCE) 15 July 1970 (1970-07-15) page 1, line 10 - line 22	1-3
X	FR 2 248 842 A (HISAMITSU PHARMACEUTICAL CO) 23 May 1975 (1975-05-23) see intermediate (IV) p.1 page 1, line 37 -page 2, line 3	1-3
X	SPANO R., LINARI G., MARRI R.: BOLLETTINO CHIMICO FARMACEUTICO, vol. 109, no. 8, 1970, pages 485-489, XP002186934 table 1	1-3
X	US 6 022 884 A (JOSEY JOHN A ET AL) 8 February 2000 (2000-02-08) tables 8-13, col.84-91. claim 1	1-3,14
X	EP 1 054 004 A (YAMANOUCHI PHARMA CO LTD) 22 November 2000 (2000-11-22) claim 1	1-3
Y	WO 99 65897 A (RAMURTHY SAVITHRY ;CHIRON CORP (US); GOFF DANE (US); NUSS JOHN M () 23 December 1999 (1999-12-23) page 1, line 5 - line 13; claims 1,27,73,84	1-16
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Y	example 129 p.67;example 44 p.38; example 140 p.72.	1-16

INTERNATIONAL SEARCH REPORT

Int. application No.
PCT/EP 02/12067

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty (see D1-D6). So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a complete search over the whole breadth of the claims 1-3 is impossible. Consequently, the search has been restricted to the compounds of claims 1(part)-3(part), 4-16 and to those given in the examples of the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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